



Efficacy and Safety of Cromolyn Sodium Ophthalmic Solution with and without Preservative in Allergic Conjunctivitis

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Purpose: To evaluate the safety and efficacy of cromolyn sodium ophthalmic solution without preservative (Allergo-COMOD) compared with cromolyn sodium ophthalmic solution with preservative (Allergocrom) for the treatment of allergic conjunctivitis. **Patients and Methods:** Forty-seven patients with allergic conjunctivitis were randomly assigned to one of two treatment groups: Allergo-COMOD or Allergocrom four times daily. Data were collected at screening, baseline, and after one week and two weeks of therapy. Changes in main eye symptom score (MESS), the object change of signs determined by investigators, in particular regarding ocular itching or conjunctival redness, and any adverse events were analyzed. **Results:** The symptoms of subjects in both treatment groups achieved almost maximum improvement after one week of treatment, and remained stable during the treatment period. There was no difference in MESS reduction between the Allergo-COMOD and Allergocrom groups. No differences were noted between the two groups by the clinical investigators' evaluations. There were also no significant adverse events throughout the study period. **Conclusions:** An Allergo-COMOD eye drop four times per day used in this study demonstrated satisfactory safety and efficacy features in the treatment of allergic conjunctivitis, when Allergocrom was used in the control group.

Key words: cromolyn sodium, allergic conjunctivitis, preservative

INTRODUCTION

Perennial allergic conjunctivitis is characterized by the presence of allergic ocular symptoms throughout the year, and is thus distinguished from seasonal allergic conjunctivitis^{1,2}. This disease is induced by IgE-related, type I hypersensitivity reactions mediated by degranulated mast cells, and the most common cause is the household dust mite^{3,4}. The predominant symptom of allergic conjunctivitis is red itchy eyes. It has been shown that histamine induces itching on the ocular surface via H1 receptors and redness via both H1 and H2 receptors⁵⁻⁷. The disease is also often accompanied by nasal symptoms of rhinitis. Clinically, antihistamine, steroid, and mast cell stabilizer drugs have been used to treat the disease, and one such mast cell stabilizer is cromolyn sodium.

Cromolyn sodium is a mast cell stabilizer that acts by inhibiting both the degranulation of sensitized mast cells

and the release of histamine from conjunctival mast cells⁸. Cromolyn sodium 2% ophthalmic solutions have been launched and are indicated for the treatment of allergic ocular disease. However, these topical eye drops are often not well tolerated because of the irritation caused by the preservative in the formulation. Therefore, a new formulation containing the active ingredient without the addition of preservative is deemed preferable. To achieve this goal, the key alternative is to pack the ophthalmic solution in an aseptic bottle. The objective of this study was to investigate whether the efficacy and safety profile of cromolyn sodium without preservative (Allergo-COMOD®) is equivalent to that of cromolyn sodium with preservative (Allergocrom®).

PATIENTS AND METHODS

The trial was conducted between July 21, 2005, and November 10, 2005, at the Department of Ophthalmology, Tri-Service General Hospital, Taipei, Taiwan.

Subjects

Patients included in the study were aged between 10 and 70 years, and had suffered perennial allergic conjunctivitis for at least one year. Perennial allergic conjunctivitis was defined by a documented record of a positive skin prick test

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or radioallergosorbent test (RAST), or diagnosis by contact allergy patch (CAP). The inclusion criteria also required subjects to have a main eye symptom score (MESS) of ≥ 3 assessed at baseline and to discontinue the use of contact lenses during the entire study period. The methods used to quantify allergic ocular symptoms were similar to those previously reported⁹. The MESS was equal to the sum of clinical scores for itching and conjunctival redness, each assessed on a four-point scale (0=none, 1=mild, 2=moderate, 3=severe symptoms). Exclusion criteria were a diagnosis of seasonal allergic conjunctivitis or any ocular disorder other than allergic conjunctivitis; a history of ocular surgery within the three months before the study; a history of severe persistent asthma, retinal detachment, diabetic retinopathy, or rheumatoid arthritis; the use of prohibited medications (corticosteroids, nonsteroidal anti-inflammatory drugs, antihistamines, mast cell stabilizers, immunosuppressants, topical ocular vasoconstrictors, and other topical eye drops) during the study or within seven days before the screening visit; a history of hypersensitivity to cromolyn or any component of the study medications; pregnancy, lactation, or childbearing potential in premenopausal subjects; a history of alcohol or drug abuse; participation in an investigational drug trial within four weeks before entering this study; and any other serious disease considered by the investigator to be incompatible with entry into the trial.

Study Design

Patients meeting the inclusion criteria at the end of screening and randomization were allocated to receive treatment with either cromolyn sodium 2% ophthalmic solution without preservative (Allergo-COMOD) or cromolyn sodium 2% ophthalmic solution with preservative (Allergocrom) in a randomized, double-blind, parallel-group study. Treatment allocation was determined by the following procedure. A subject randomization number was assigned sequentially to eligible subjects who met all the inclusion criteria and no exclusion criteria. Each type of eye drop was also assigned a number randomly and allocated to the subject with the same number. All researchers were blinded to treatment allocation until all data had been collected.

Treatment Interventions

Patients were instructed to instill an eye drop into the affected eye(s) four times daily at 9 am, 1 pm, 5 pm, and 9 pm. If both eyes of the same patient met the inclusion criteria, they were both treated with the same medication.

Procedures

Subjects who had read and signed the informed consent form were scheduled to attend the clinic for a screening visit (visit 1). At the screening visit, demographic information and a medical history, including any history of concurrent ocular and nonocular disease and concomitant therapy, were collected. All subjects were screened by the study investigator using the inclusion and exclusion criteria.

The study medications were administered from the day 0 visit (visit 2) and the randomization procedure was performed at the same time. At the day 0 visit, the baseline MESS was recorded before the drug was administered. Subjects were instructed to return on day 7 ± 3 after the study medication was administered (visit 3). Efficacy evaluation (MESS) and safety information, including changes in concomitant medications and adverse events, were recorded at this visit.

The final visit was scheduled for day 14 ± 3 (visit 4). The efficacy of the treatment, including MESS and global assessment, and safety information, including an ocular status examination, were evaluated and the subjects were dismissed from the study at this visit.

Efficacy

The primary efficacy variable was net change in MESS at the last evaluation compared with baseline. The secondary efficacy variables were: (1) net change in MESS after the first week of treatment compared with baseline; (2) net change in the symptom score for itching after the first and second weeks of treatment compared with baseline; (3) net change in the symptom score for conjunctival redness after the first and second weeks of treatment compared with baseline; and (4) the investigator's global impression.

Safety

The safety profile was evaluated with the following measures: (1) incidence of adverse events; (2) changes in physical characteristics; (3) changes in ophthalmic characteristics, including visual acuity, intraocular pressure, and fundus parameters; (4) net change from baseline in laboratory test results; and (5) net change from baseline in vital signs.

Statistical Analyses

The primary endpoint, net change in MESS at the last evaluation compared with the baseline MESS, was analyzed using analysis of covariance (ANCOVA), with the appropriate baseline value as covariate. Net change in each other efficacy score was analyzed with the same ANCOVA method to compare treatments. Global assessment by the

Table 1 Summary of demographic characteristics-ITT

Demographic Characteristic		Treatment Group		Total	p-value
		Allergo-COMOD	Allergocrom		
Age (years)	N	23	24	47	0.77 ₁
	Mean (SD)	35.3 (8.7)	34.4 (7.6)	34.8 (8.1)	
	Median (IQR)	34.0 (11.0)	33.0 (8.0)	34.0 (9.0)	
	Min-Max	24~55	27~58	24~58	
Weight (kg)	N	23	24	47	1.00 ₁
	Mean (SD)	62.6 (13.4)	61.2 (10.1)	61.8 (11.7)	
	Median (IQR)	56.0 (21.0)	59.5 (11.0)	59.0 (17.0)	
	Min-Max	47~96	47~83.5	47~96	
Height (cm)	N	23	24	47	0.86 ₂
	Mean (SD)	165.4 (7.5)	165.0 (6.5)	165.2 (6.9)	
	Median (IQR)	165.0 (11.5)	165.0 (10.0)	165.0 (10.0)	
	Min-Max	150~177	155~179	150~179	
BMI (kg/m ²)	N	23	24	47	0.95 ₁
	Mean (SD)	22.74 (3.73)	22.34 (2.44)	22.54 (3.11)	
	Median (IQR)	21.88 (4.13)	21.92 (3.08)	21.88 (3.90)	
	Min-Max	17.92~31.53	19.53~28.34	17.92~31.53	
Sex	Male N (%)	11 (47.8%)	14 (58.3%)	25 (53.2%)	0.56 ₃
	Female N (%)	12 (52.2%)	10 (41.7%)	22 (46.8%)	

1: Wilcoxon ranked-sum test

2: Two sample t-test

3: Fisher's exact test

investigator was analyzed using the Mantel-Haenszel test. All efficacy variables are reported as the appropriate point estimate and the 95% confidence interval (CI). P values were calculated for all comparison tests.

Adverse events are reported according to treatment groups and physiological systems, as appropriate. Differences in the incidence of adverse events between treatment groups were analyzed with Fisher's exact test. Net changes in vital signs and laboratory test results from baseline values were analyzed by descriptive statistics and ANCOVA. Changes in physical and ophthalmic examination results are given for each individual system. All statistical tests used were two-tailed, with $\alpha = 0.05$.

RESULTS

We planned to enroll about 25 subjects per group. At the end of the study, 47 subjects were randomized, such that 23 subjects were assigned to the Allergo-COMOD group and 24 subjects received Allergocrom. All randomized subjects were included in the intent-to-treat (ITT) population. Except for one subject, who could not be confirmed to have completed at least 11 days of treatment and was therefore excluded, all subjects were considered to be evaluable as the per-protocol (PP) population.

Table 2 Statistical analysis of change from baseline to the last visit on MESS

Statistics	Treatment Group		Difference [95% CI] ₂
	Allergo-COMOD	Allergocrom	
ITT population			
N	23	24	
Mean (SD)	1.91 (0.42)	1.83 (0.64)	0.17
Median (IQR)	2.0 (0.0)	2.0 (0.0)	[-0.14; 0.47]
Min-Max	1.0 - 3.0	0.0 - 3.0	
95% CI ₁	[1.74; 2.17]	[1.58; 2.00]	
PP population			
N	22	24	
Mean (SD)	1.91 (0.43)	1.83 (0.64)	0.17
Median (IQR)	2.0 (0.0)	2.0 (0.0)	[-0.15; 0.48]
Min-Max	1.0 - 3.0	0.0 - 3.0	
95% CI ₁	[1.73; 2.18]	[1.58; 2.00]	

1: Two-sided 95% CI of the mean based on ANCOVA

2: Allergo-COMOD minus Allergocrom; two-sided 95% CI of LS-mean difference based on ANCOVA

Demographic Characteristics of All ITT Subjects

The characteristics of the study subjects are shown in Table 1. The mean age of all ITT subjects was 34.83 years and the difference between the two treatment groups was not statistically significant ($P=0.77$). Eleven female subjects and 12 male subjects were in the Allergo-COMOD group, and 14 female subjects and 10 male subjects were in the Allergocrom group. No statistically significant treatment disparity was found in the distributions of the sexes ($P=0.56$). Mean heights and weights were similar between the treatment groups. Mean weight/height in the Allergo-COMOD group was 62.57 kg/165.35 cm and in the Allergocrom group was 61.15 kg/165.00 cm. The body mass index was 22.74 kg/m² in the Allergo-COMOD group and 22.34 kg/m² in the Allergocrom group. Height, weight, and BMI were thus similar in the two treatment groups.

Efficacy Analysis

Both treatments showed obvious potent effects in terms of reducing MESS (Table 2). Reductions in MESS (mean $\pm$ SD) of 1.91 ± 0.42 (95% CI, 1.74-2.17) for the ITT population and 1.91 ± 0.43 (95% CI, 1.73-2.18) for the PP population were observed in the Allergo-COMOD group. Similar results were observed for the Allergocrom group (1.83 ± 0.64 for both the ITT and PP populations). The two-sided 95% CIs for MESS reductions for both treatment groups indicated statistically significant decrements in MESS because these two intervals did not contain zero.

Net change in MESS from baseline in the first week of

Table 3 Statistical analysis of change from baseline to the 1st week visit on MESS

Statistics	Treatment Group		Difference [95% CI] ₂
	Allergo-COMOD	Allergocrom	
ITT population			
N	22	24	
Mean (SD)	1.77 (0.53)	1.92 (0.28)	0.38
Median (IQR)	2.0 (0.0)	2.0 (0.0)	
Min-Max	0.0 - 2.0	1.0 - 2.0	[-0.35; 0.14]
95% CI ₁	[1.62; 1.97]	[1.73; 2.07]	
PP population			
N	21	24	
Mean (SD)	1.76 (0.54)	1.92 (0.28)	0.35
Median (IQR)	2.0 (0.0)	2.0 (0.0)	[-0.37; 0.13]
Min-Max	0.0 - 2.0	1.0 - 2.0	
95% CI ₁	[1.60; 1.96]	[1.73; 2.07]	

1: Two-sided 95% CI of the mean based on ANCOVA

2: Allergo-COMOD minus Allergocrom; two-sided 95% CI of LS-mean difference based on ANCOVA

treatment was included as one of the secondary efficacy endpoints (Table 3). Similarly to the primary efficacy results, both treatments showed obvious reductions in MESS. The mean changes in MESS after the first week of Allergo-COMOD and Allergocrom were 1.77 ± 0.53 and 1.92 ± 0.28 , respectively, for the ITT population ($P=0.382$), and 1.76 ± 0.54 and 1.92 ± 0.28 , respectively, for the PP population ($P = 0.352$). Thus, no treatment difference was found in either the ITT or PP populations. Because the 95% CIs for reduction in MESS in the first week did not contain zero, both treatments showed significant effects in the treatment of subjects with allergic conjunctivitis. According to the trends in MESS, the symptoms of subjects in both treatment groups achieved almost maximum improvement after one week of treatment, and remained stable during the subsequent treatment period.

Net changes in individual symptom scores in the first and second weeks of treatment relative to baseline values are presented in Figure 1 and Figure 2. No statistically significant differences were found in the symptom scores of the two treatment groups, and the P values of treatment comparisons ranged from 0.174 to 0.574. The severity of itching and conjunctival redness improved from moderate to mild for most subjects.

The study investigators assessed the subjects' overall improvement in the symptoms of allergic conjunctivitis based on the subjects' signs and sensations at the final visit. By reviewing the statistical results presented in Table 4, the global assessment showed slightly better results for the

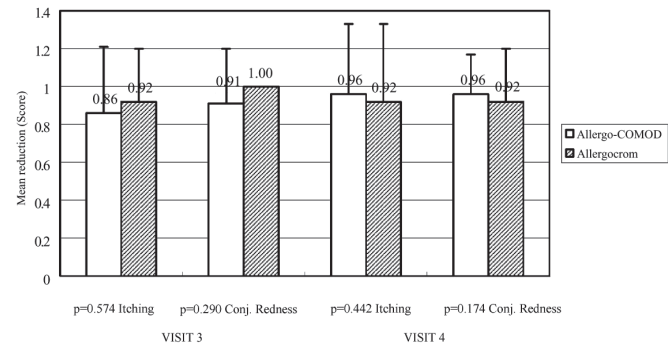


Fig. 1 Changes (Mean $\pm$ SD) from baseline (Visit 2) to Visit 3 and to Visit 4 on individual symptom score-ITT.

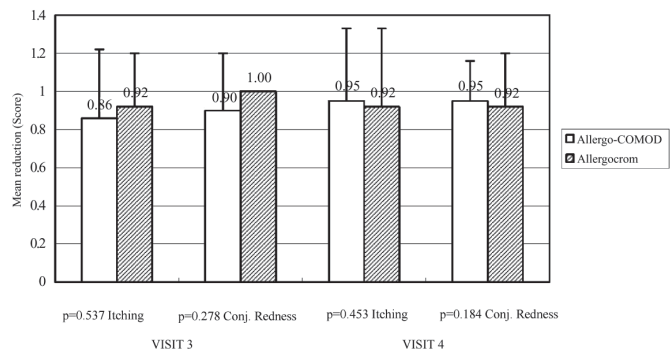


Fig. 2 Changes (Mean $\pm$ SD) from baseline (Visit 2) to Visit 3 and to Visit 4 on individual symptom score-PP.

Allergo-COMOD group compared with the Allergocrom group, in that about 24% more Allergo-COMOD-treated subjects were rated as having a “satisfactory clinical response” on the investigators’ evaluation. However, there was no significant difference between the two groups on the Mantel–Haenszel test. The P values for the treatment comparisons of the ITT and PP populations were 0.083 and 0.109, respectively. These results again demonstrate that most subjects received significant benefits from treatment with either of the study therapies.

Safety Analysis

The mean daily dose was calculated as the average weight of eye solution used divided by the total days of exposure to treatment. The mean duration of exposure was calculated as the total number of days for all subjects exposed to the study medicine, divided by the number of subjects. Forty-seven subjects were studied in this trial with a fairly balanced treatment assignment, with 23 administered Allergo-COMOD and 24 Allergocrom. Both treatment periods were 14 days. The mean duration of

Table 4 Statistical analysis of global assessment by the investigators

Category	Treatment Group		Total	p-value ¹
	Allergo-COMOD	Allergocrom		
ITT population				
Clinical cure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.09
Satisfactory clinical response	17 (73.9%)	12 (50.0%)	29 (61.7%)	
Slight clinical improvement	5 (21.7%)	9 (37.5%)	14 (29.8%)	
Clinically unchanged	1 (4.3%)	3 (12.5%)	4 (8.5%)	
Total	23 (100.0%)	24 (100.0%)	47 (100.0%)	
PP population				
Clinical cure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.11
Satisfactory clinical response	16 (72.7%)	12 (50.0%)	28 (60.9%)	
Slight clinical improvement	5 (22.7%)	9 (37.5%)	14 (30.4%)	
Clinically unchanged	1 (4.5%)	3 (12.5%)	4 (8.7%)	
Total	22 (100.0%)	24 (100.0%)	46 (100.0%)	

1: Mantel-Haenszel test

exposure (including the day of last administration) per subject was 13.73 ± 2.10 days for Allergo-COMOD and 13.67 ± 0.96 days for Allergocrom. The unit dose of the test drug was one drop of eye solution (about 0.025 mL or 0.025 g), and the total daily dose was ideally about 0.2 g (from administration q.i.d. for both eyes). Subjects in the Allergo-COMOD group were treated with a median dose of 0.21 g/day and those in the control group with 0.22 g/day. This information suggests that about 0.2 g of both Allergo-COMOD and the control drug were used by the subjects in this study.

Only one event of mild eye pain was reported in a single (4.3%) Allergo-COMOD-treated subject. No other adverse event was reported during the entire study period. No statistically significant difference was observed between treatment groups in the final laboratory examination results. All vital signs were stable throughout the study for both treatment groups. The results of physical examinations remained unchanged in all subjects in both treatment groups. The results of ocular examinations were unchanged from baseline to the posttreatment visit for both groups.

DISCUSSION

Allergo-COMOD (cromolyn sodium 2% ophthalmic solution without preservative) has been registered for the

treatment of allergic conjunctivitis in Taiwan. The primary aim of this clinical trial was to study the efficacy and safety of Allergo-COMOD eye drops given four times daily for two weeks compared with those of Allergocrom given four times daily, in subjects suffering from allergic conjunctivitis. The Allergo-COMOD eye drop used in this study demonstrated satisfactory safety and efficacy features for the treatment of allergic conjunctivitis compared with those of Allergocrom.

The primary endpoint of this study measured the mean changes in MESS from baseline to the final visit. The P value for the mean treatment comparison on the primary endpoint did not indicate the superiority of Allergo-COMOD compared with Allergocrom. However, both treatments did cause a dramatic drop in MESS. For the ITT population, MESS decreased in the Allergo-COMOD group by 1.91 ± 0.42 (95% CI, 1.74-2.17) and in the Allergocrom group by 1.83 ± 0.64 (95% CI, 1.58-2.00). Similar results were observed for the PP population. All these analyses demonstrate the efficacious effects of Allergo-COMOD and Allergocrom in alleviating the signs and symptoms of allergic conjunctivitis. Secondary efficacy endpoints were used in this study as auxiliary evaluations of efficacy. Most of the secondary analysis results were consistent with the primary analysis results, in which the potent effects of Allergo-COMOD and Allergocrom were clear. Statistical tests revealed no treatment differences in any of the secondary variables. Previous reports have noted that topical cromolyn solution is effective in treating allergic conjunctivitis¹⁰⁻¹³. Our results show that topical cromolyn solution without preservative is as effective as that with preservative.

Van Bijsterveld¹⁰ and Vakil et al.¹⁴ have reported that topical cromolyn solution is a safe eye drop for allergic conjunctivitis, without significant side effects. Our data show similar results. Regarding the incidence of adverse effects, only one event of mild eye pain was reported in an (4.3%) Allergo-COMOD-treated subject. No other adverse events were reported during the entire study period. No statistically significant differences between the treatment groups were observed in the final laboratory examination results. All vital signs were stable throughout the study in both treatment groups. The physical examination results for all subjects remained unchanged in both treatment groups. The results of ocular examinations were unchanged from baseline to the post-treatment visit for both groups.

From previous studies, it appears that the preservative may be largely responsible for the allergic, toxic, or inflammatory reactions induced by topical drugs. Noecker et al. found less damage to the cornea and lower levels of

inflammatory infiltrates in the conjunctiva after treatment with drugs containing the lowest preservative concentrations in animal models¹⁵. A survey performed on 3090 patients with allergic conjunctivitis by 507 general practitioners noted better compliance and fewer adverse effects in the "preservative-free" group than in the "preservative" group¹⁶. Although our results show that there were no differences in adverse effects in the Allergo-COMOD and Allergocrom groups, we believe that preservative-free eye drops may be safer than eye drops containing preservative because less interleukin-1 β is induced¹⁷, better tear stability and corneal barrier function are maintained¹⁸, and apoptosis rates are lower in conjunctival cells¹⁹.

An Allergo-COMOD eye drop administered four times per day, as used in this study, has been shown to have satisfactory safety and efficacy features in the treatment of allergic conjunctivitis, when Allergocrom was used in the control group. This study confirms that Allergo-COMOD and Allergocrom eye drops administered four times daily are similar in both their therapeutic efficacy profiles and safety considerations.

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