Efficacy of olopatadine hydrochloride 0.1%, emedastine difumarate 0.05%, and loteprednol etabonate 0.5% for Chinese children with seasonal allergic conjunctivitis: a randomized vehicle-controlled study

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Background: Allergic conjunctivitis (AC) is a disease of various agents that affects the physical and mental health of children. Although the most effective therapy has not been found so far, it is essential to explore the considerable therapeutic method. We compared the clinical efficacy of olopatadine, emedastine, loteprednol etabonate (LE), and vehicle for treating seasonal allergic conjunctivitis (SAC) in Chinese children.

Methods: Eighty cases of 160 eyes aged from 5 to 10 years with SAC were available and those subjects were randomly distributed into 4 groups. Both their eyes received olopatadine hydrochloride 0.1% twice a day, emedastine difumarate 0.05% twice a day, or LE 0.5% 4 times a day, respectively, whereas those of the control group received artificial tears (AT) 0.5% 3 times a day. The study was conducted successfully and the observations were collected before treatment and on day 8 (±1 day) and day 15 (±2 days) afterward. The principal measurement of efficacy was focused on the signs and symptoms of the subjects, evaluated before and after treatment, in addition to visual acuity (VA) and fundus oculi.

Results: On day 8 (±1 day) and day 15 (±2 days), all the antiallergic agents were found to be more effective than vehicle (p < 0.05) in terms of all symptoms and signs. However, there was no statistical significance (p ≥ 0.05) shown among the treatment groups. There were no evident changes in VA and no clinically significant changes were observed in fundus oculi.

Conclusion: After the treatment, the efficacy presented a similar distribution among the trial groups. © 2016 The Authors International Forum of Allergy & Rhinology, published by ARSAAOA, LLC.

Key Words: SAC; olopatadine hydrochloride; emedastine difumarate; LE; vehicle; efficacy

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respectively compares them with olopatadine 0.1%. We mainly focus on comparing olopatadine, emedastine, LE, and vehicle (AT) in the temporary treatment of Chinese children with SAC in similar living environments.

**Patients and methods**

**Study design**

This was a 3-visit, prospective, single-blind, randomized, placebo-controlled, single-center study in the Ophthalmology Department of the Second Hospital affiliated with Dalian Medical University. There were 90 subjects (180 eyes) of SAC primarily in the study. We finally had 80 children of 160 eyes (48 cases of boys, 32 girls, ranging from 5 to 10 years old, with an average age of 6.33 ± 1.89 years); another 10 cases were excluded due to loss to follow-up. Registration of children with SAC took place from July 2015 through November 2015 in our study. Before study procedures were conducted, written informed consent was obtained from all parents/guardians. The study protocol was approved by the Ethics Committee of Second Hospital affiliated with Dalian Medical University.

**Study subjects**

The following were all the criteria of our study: the age of children ranging from 5 to 10 years old; stopping using other anti-allergy agents for at least 30 days; with grade 3 or higher in symptoms and grade 2 or higher in signs at visit 1 (the first study visit). All the variables with respect to baseline were similar in each group. Changes of symptoms were graded on a 0 to 4 scale and increased by 0.5 increments; the higher the points the more evident the symptoms were. Ocular symptoms were graded on a 0 to 4 scale (0 = absent, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe). The main symptoms include itching, photophobia, foreign body sensation, and blinking. The assessment of grade is shown in Table 1. The main signs include conjunctival papilla, follicle, conjunctival congestion, and conjunctival edema. Ocular signs were graded on a 0 to 3 points, similar to the definition of symptoms (0 = absent, 1 = mild, 2 = moderate, and 3 = severe). The evaluation of grading is shown in Table 2. The measurement standard of the symptoms and signs was evaluated by the same investigator through the direct questioning of children or observation. All the efficacy variables were assessed for both eyes at each visit.

Exclusion criteria: aged ≥11 years or ≤4 years old. Children who suffered from refractive errors, those whose best corrected VA was ≤0.4, or those children who suffered from keratoconus were also excluded. In addition, those who had received an ocular operation or who wore intraocular lens or contact lenses were excluded. Outpatients with intraocular pressure > 21 mm Hg in any eye were also excluded. Further exclusions were children using any antiallergic medication (such as H-1 antihistamines, mast cell stabilizers, eye drops of corticosteroid, nasal spray, or general drugs) in the 30 days before testing. Using any drugs that cause eye diseases, any anti-allergic treatment, other ocular diseases and systemic diseases, other active eye diseases and diseases of the heart, brain, liver, kidney, or hematopoietic system in the last 1 month also were disqualified in outpatient selection. Those who were unable to assess the efficacy or failed to offer information completely were excluded. Finally, those who were not using the ophthalmic solution regularly, or not following-up, thus affecting the curative effect, were also excluded.

**Study procedures**

The subjects were distributed into 4 groups by random number table; on average, 20 cases in each group. Children were randomly assigned to receive topical administration of 1 drop of olopatadine hydrochloride (HCL) 0.1% ophthalmic solution (Patanol) twice per day (BID) (olopatadine solution group); 1 drop of emedastine difumarate 0.05% ophthalmic solution (Emadine) BID (emedastine solution group); LE 0.5% ophthalmic suspension (Lotemax) 4 times per day (QID) (LE solution group); or AT 0.5% (Refresh Plus) 3 times per day (TID) (vehicle group); in both eyes for 14 ± 2 days. Ophthalmic solution was dropped into the fornix conjunctivae inferior for 1 drop in each eye.

A visit 1 (day 0), on the first day of the study, all patients were questioned about ethnicity; systemic allergic conditions or not, and family members (father, mother, grandfather, grandmother, etc.) with atopic history

| Score | Severity | Description                        |
|-------|----------|------------------------------------|
| 0     | Absent   | Without any symptoms               |
| 1     | Slight   | Slight symptoms, patients having little or slight feeling |
| 2     | Mild     | Mild symptoms, patients feeling discomfort but being capable of tolerating |
| 3     | Moderate | Moderate symptoms, patients being difficult to tolerate |
| 4     | Severe   | Severe symptoms, patients being incapable of tolerating |

*The main symptoms include itching, photophobia, blinking.

**TABLE 1. The scoring system of eye symptoms**

| Score | Severity | Description                        |
|-------|----------|------------------------------------|
| 0     | Absent   | Without any symptoms               |
| 1     | Mild     | Mild signs                          |
| 2     | Moderate | Moderate signs                      |
| 3     | Severe   | Severe signs                        |

*The main signs include conjunctival papilla, follicle, conjunctival congestion, edema.

**TABLE 2. The scoring system of eye signs**
including suffering from allergic rhinitis, asthma, eczema, dermatitis, food allergy, and drug allergy. Moreover, they were asked whether, in their living environment, there were pets or not; and whether they had done allergen detection (especially plant, pollen, dust mites, and animal dander) in the past or not. Furthermore, naked VA and the best corrected VA were measured carefully, VA was observed through the international standard E vision table and all the children used the same VA chart. In addition, ocular signs were tested through slit lamp examination. Fundus preset lens was also through the slit lamp. Ocular symptoms were evaluated through query direct of the children by the investigator. All the inspections were completed by the same operator. The investigator was blinded to what ophthalmic solution the children were taking upon their treatment. Ocular symptoms and signs, VA, and fundus preset lens examination was also collected during visit 2 (day 7 ± 1) and visit 3 (day 14 ± 2).

Statistics analysis
The SPSS 21.0 software program (IBM Corp., Armonk, NY) was used to perform the statistical analysis. The symptoms and signs of objects were consistent with homogeneity of variance by Levene test. Descriptive statistics were applied in studying population characteristics. Data were summarized and presented as the number of collection, percentages, mean and standard deviation (SD). The variables of symptoms and signs from baseline were used in this randomized and vehicle-controlled study, analysis of covariance (ANCOVA) model with double side test. They were expressed as mean, SD, 95% confidence interval (CI), and p value. A p value of ≤0.05 was considered as statistically significant. VA and fundoscopy were descriptively summarized.  

Results
General clinical characteristics
For the olopatadine group, the mean age of the children was 6.35 ± 2.01 years and 65% were boys. In the emedastine group, the mean age was 6.37 ± 1.95 years and 70% were boys. The mean age of children in the LE group was 6.40 ± 1.99 years, 50% of whom were boys; the mean age of the children from the vehicle group was 6.33 ± 1.80 years, 55% of whom were boys. The general characteristics of children between the treatment groups and the control group were well-balanced (Table 3). None of the remaining participants withdrew during the study.

Treatment efficacy
Trial groups presented a similar efficacy in symptoms
Table 4 shows the changes of ocular symptoms from baseline of the drug groups compared with those of the placebo group after 2 weeks of treatment. After 1 week, changes in ocular itching, blinking of eyes, and photophobia were statistically significant (p < 0.05) between the study groups and the placebo group. There were no statistically significant differences among the treatment groups (p > 0.05). After 2 weeks of treatment, the changes in ocular itching, blinking of eyes, and photophobia were statistically significant between the study groups and the vehicle group (p < 0.05), and there were no statistically significant differences among the treatment groups (p > 0.05).

Trial groups presented a similar efficacy in signs
Table 5 expresses the grades of SAC for all the tests in ocular signs after 2 weeks of treatment. For all the signs, there were no statistically significant differences among the treatment groups (p > 0.05), and the differences between the treatment groups and the control group were statistically significant (p < 0.05).

VA and fundus oculi
No clinically significant changes were found in VA from the baseline and no changes were found in fundus oculi among all the groups in each observation.

Discussion
For patients who suffer from ocular discomfort, with AC, their quality of life is affected to a certain degree and their families may be economically burdened.  As for children, when visiting doctors, the parents sometimes mistakenly assume that their children have hyperkinetic, to some extent, which can affect the physical and mental health of children. So it is essential to explore a safe, effective, short-term, and proper therapeutic drug to manage the AC.

The novelty of the present trial lies in that it is the first time the efficacy of olopatadine hydrochloride 0.1%, emedastine difumarate 0.05%, and LE 0.5% ophthalmic suspension has been compared among the 3 drugs. To the best of our knowledge, olopatadine hydrochloride 0.1% has been compared to emedastine difumarate 0.05%,  LE 0.5% ophthalmic suspension, and placebo with each other, respectively, in efficacy. Emedastine difumarate 0.05% has been compared with vehicle to assess efficacy. In addition, LE 0.5% ophthalmic suspension has been compared with placebo to evaluate efficacy. However, emedastine difumarate 0.05% and LE 0.5% ophthalmic suspension have not been compared with each other, while on that basis we put forward with these 2 eye drops compared to olopatadine hydrochloride 0.1%, respectively.

After the treatment, ocular signs and symptoms that appeared in our study may be related to the following reasons: (1) in this trial the control group was AT, some of which offered alleviation through lubricating the ocular surface and raised humidity or glutinosity factors to salt solution; (2) AT may improve the barrier function of the ocular surface, which is useful in the treatment of SAC; (3) compliance of guardians/parents and children was
### TABLE 3. Demographic characteristics of the study population

|                           | Olopatadine (n = 20) | Emedastine (n = 20) | LE (n = 20) | Vehicle (n = 20) | Total (n = 80) |
|---------------------------|----------------------|---------------------|-------------|------------------|---------------|
| **Age (years), mean ± SD**| 6.35 ± 2.01          | 6.37 ± 1.95         | 6.40 ± 1.99 | 6.33 ± 1.80      | 6.33 ± 1.89   |
| **Gender, n (%)**         |                      |                     |             |                  |               |
| Boys                      | 13 (65.00)           | 14 (70.00)          | 10 (50.00)  | 11 (55.00)       | 48 (60.00)    |
| Girls                     | 7 (35.00)            | 6 (30.00)           | 10 (50.00)  | 9 (45.00)        | 32 (40.00)    |
| **Ethnicity, Chinese, n (%)** | 20 (100)            | 20 (100)            | 20 (100)    | 20 (100)         | 80 (100)      |
| **AC duration, n (%)**    |                      |                     |             |                  |               |
| < 6 months                | 10 (50.00)           | 8 (40.00)           | 7 (35.00)   | 5 (25.00)        | 30 (37.50)    |
| ≥ 6 months                | 10 (50.00)           | 12 (60.00)          | 13 (65.00)  | 15 (75.00)       | 50 (62.50)    |
| **Allergen detection, n (%)** | 1 (5.00)            | 3 (15.00)           | 3 (15.00)   | 1 (5.00)         | 8 (10.00)     |

AC = allergic conjunctivitis; SD = standard deviation.

### TABLE 4. The ocular symptoms changing from baseline after 2 weeks of treatment (based on the uniform diagnostic criteria)*

|                   | Mean ± SD | Olopatadine (n = 20) | Emedastine (n = 20) | LE (n = 20) | Vehicle (n = 20) |
|-------------------|-----------|----------------------|---------------------|-------------|------------------|
| **Olopatadine**   |           |                      |                     |             |                  |
| Itching           | 0.28 ± 0.64| —                    | 0.581 (−0.21 to 0.37)| 0.096 (−0.44 to 0.52)| 0.030 (−0.73 to 0.16) |
| Photophobia       | 0.35 ± 0.43| —                    | 0.925 (−0.23 to 0.20)| 0.075 (−0.02 to 0.41)| 0.000 (−0.70 to −0.27) |
| Blinking          | 0.20 ± 0.30| —                    | 0.243 (−0.28 to 0.07)| 0.902 (−0.19 to 0.17)| 0.002 (−0.47 to −0.11) |
| **Emedastine**    |           |                      |                     |             |                  |
| Itching           | 0.13 ± 0.39| 0.581 (−0.37 to 0.21)| —                    | 0.269 (−0.13 to 0.45)| 0.000 (−0.81 to 0.24) |
| Photophobia       | 0.38 ± 0.36| 0.925 (−0.20 to 0.22)| —                    | 0.062 (−0.01 to 0.42)| 0.000 (−0.69 to 0.26) |
| Blinking          | 0.30 ± 0.38| 0.243 (−0.07 to 0.28)| —                    | 0.298 (−0.09 to 0.27)| 0.04 (−0.36 to 0.01) |
| **LE**            |           |                      |                     |             |                  |
| Itching           | 0.05 ± 0.22| 0.096 (−0.52 to 0.04)| 0.269 (−0.45 to 0.13)| —           | 0.000 (−0.97 to 0.40) |
| Photophobia       | 0.08 ± 0.24| 0.075 (−0.41 to −0.02)| 0.062 (−0.42 to 0.01)| —           | 0.000 (−0.90 to −0.46) |
| Blinking          | 0.13 ± 0.28| 0.902 (−0.17 to 0.19)| 0.298 (−0.27 to 0.09)| —           | 0.003 (−0.46 to −0.10) |
| **Vehicle**       |           |                      |                     |             |                  |
| Itching           | 0.70 ± 0.62| 0.003 (−0.16 to 0.73)| 0.000 (−0.24 to 0.81)| 0.000 (−0.40 to 0.97)| —               |
| Photophobia       | 0.93 ± 0.69| 0.000 (0.27 to 0.70) | 0.000 (0.26 to 0.69)| 0.000 (0.46 to 0.91)| —               |
| Blinking          | 0.48 ± 0.55| 0.002 (−0.11 to 0.47)| 0.041 (−0.01 to 0.36)| 0.003 (0.10 to 0.46)| —               |

*Values are mean ± SD or p (95% CI), as indicated.
CI = confidence interval; LE = loteprednol etabonate; SD = standard deviation.

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good—they very strictly used the ophthalmic solution according to the requirements. Hence the efficacy of the treatment came out.

In the current study, compared with emedastine difumarate 0.05%, olopatadine hydrochloride 0.1% did not show a statistically significant difference ($p > 0.05$) in suppressing the symptoms and signs of SAC and it was consistent with the conclusion obtained by Borazan et al.\textsuperscript{13}

Olopatadine hydrochloride 0.1% solution displayed no obvious superiority when compared to LE 0.5% ophthalmic suspension, which was in agreement with Gong et al.,\textsuperscript{14} who reported that LE ophthalmic suspension 0.5% compared with olopatadine hydrochloride 0.1% was inferior in 300 patients. On the contrary, Berdy et al.\textsuperscript{28} reported that olopatadine hydrochloride 0.1% was superior to LE hydrochloride...
In relief of the symptoms and signs of SAC, olopatadine hydrochloride 0.1% ophthalmic solution compared with vehicle, the difference was statistically significant \((p < 0.05)\). Our study was consistent with that of McLaurin et al.\(^2\) and Mah et al.,\(^2\) who reported how olopatadine hydrochloride 0.1% ophthalmic solution compared with placebo. In their reports, olopatadine hydrochloride 0.1% ophthalmic solution was more effective in reducing ocular symptoms and signs of patients suffering from AC. The results of olopatadine hydrochloride 0.1% ophthalmic solution compared with placebo may be that the control agent was AT, though it may water down the allergen from eyes and serve as a barrier to additional exposure by keeping the allergen from adhesion to the ocular surface,\(^3\) whereas olopatadine hydrochloride 0.1% is a dual-action agent.

In the current study, emedastine difumarate 0.05% was superior to vehicle in releasing the symptoms and signs of SAC and the differences were significant \((p < 0.05)\). In a previous study, Borazan et al.\(^1\) compared the efficacy of emedastine difumarate 0.05% with placebo and highlighted that emedastine difumarate 0.05% was more effective than placebo in offering rapid relief to patients with SAC.

As for the comparison of LE hydrochloride 0.5% and vehicle, the difference was statistically significant \((p < 0.05)\). LE hydrochloride 0.5% has been demonstrated to be more effective than placebo in the treatment of SAC in an earlier study.\(^4\)

In the present study, emedastine difumarate 0.05% was equally effective with LE hydrochloride 0.5% \((p > 0.05)\) in suppressing the clinical symptoms and signs of SAC. Since this was the first time comparing them with each other, the sample size was small, with only 20 cases in each group, and the study was confined to children 5 to 10 years old, it was confirmed that emedastine and LE had no statistically significant difference in a small sample case-series research study.

The reasons of the study are as follows: olopatadine hydrochloride 0.1% is a dual-action agent; emedastine difumarate 0.05% is a H-1 receptor antagonist; LE suspension 0.5% is a new C-20 ester drug, transforming into inactive metabolites, in this case the side effect is small.\(^5\)

### TABLE 5. The ocular signs changing from baseline after 2 weeks of treatment (based on the uniform diagnostic criteria)*

|            | Olopatadine (n = 20) | Emedastine (n = 20) | LE (n = 20) | Vehicle (n = 20) |
|------------|----------------------|---------------------|------------|-----------------|
| **Mean ± SD** |                       |                     |            |                 |
| Papilla    | 0.38 ± 0.32          | —                   | 0.938 (−0.21 to 0.19) | 0.084 (−0.02 to 0.38) | 0.009 (−0.47 to −0.07) |
| Follicle   | 0.50 ± 0.28          | —                   | 0.781 (−0.41 to 0.31) | 0.183 (−0.12 to −0.61) | 0.009 (−0.85 to −0.13) |
| Redness    | 0.43 ± 0.34          | —                   | 0.466 (−0.07 to 0.16) | 0.340 (−0.06 to 0.17) | 0.000 (−0.72 to −0.49) |
| Edema      | 0.10 ± 0.26          | —                   | 0.787 (−0.12 to 0.15) | 0.287 (−0.06 to 0.20) | 0.049 (−0.26 to 0.00) |
| **Emedastine** |                     |                     |            |                 |
| Papilla    | 0.43 ± 0.37          | 0.938 (−0.19 to 0.21) | —           | 0.067 (−0.01 to 0.39) | 0.110 (−0.46 to −0.06) |
| Follicle   | 0.53 ± 0.41          | 0.781 (−0.31 to 0.41) | —           | 0.114 (−0.073 to 0.66) | 0.019 (−0.80 to −0.07) |
| Redness    | 0.45 ± 0.36          | 0.466 (−0.16 to 0.07) | —           | 0.820 (−0.14 to 0.10) | 0.000 (−0.77 to −0.01) |
| Edema      | 0.03 ± 0.11          | 0.787 (−0.15 to 0.11) | —           | 0.449 (−0.08 to 0.18) | 0.024 (−0.27 to −0.02) |
| **LE**     |                       |                     |            |                 |
| Papilla    | 0.28 ± 0.30          | 0.084 (−0.38 to 0.02) | 0.067 (−0.39 to 0.013) | — | 0.000 (−0.65 to −0.25) |
| Follicle   | 0.30 ± 0.34          | 0.183 (−0.61 to 0.12) | 0.114 (−0.07 to 0.66) | — | 0.000 (−1.09 to −0.37) |
| Redness    | 0.15 ± 0.29          | 0.340 (−0.17 to −0.06) | 0.820 (−0.13 to 0.10) | — | 0.000 (−0.78 to −0.55) |
| Edema      | 0.03 ± 0.11          | 0.287 (−0.20 to 0.06) | 0.449 (−0.19 to 0.08) | — | 0.004 (−0.33 to −0.07) |
| **Vehicle** |                       |                     |            |                 |
| Papilla    | 0.65 ± 0.37          | 0.009 (−0.07 to 0.47) | 0.011 (−0.06 to 0.46) | 0.000 (0.25 to 0.65) | — |
| Follicle   | 1.00 ± 0.99          | 0.009 (0.13 to 0.85) | 0.019 (0.07 to 0.80) | 0.000 (0.37 to 1.10) | — |
| Redness    | 0.65 ± 0.37          | 0.000 (0.49 to 0.72) | 0.000 (0.53 to 0.77) | 0.000 (0.55 to 0.78) | — |
| Edema      | 0.18 ± 0.29          | 0.049 (0.00 to 0.26) | 0.024 (0.02 to 0.27) | 0.004 (0.07 to 0.33) | — |

*Values are mean ± SD or \(p (95\% CI)\), as indicated. CI = confidence interval; LE = loteprednol etabonate; SD = standard deviation.
AT may water down the allergen from eyes and serve as a barrier for additional exposure through keeping the allergen from adhering to the ocular surface.\(^2\) In addition, the observation in the study lasts 2 weeks, which is relatively short. It is still required a long-term observation to provide a new theoretical support in the clinical study to make more patients to alleviate the pain suffering from SAC.

We have not performed conjunctival impression cytology in the study, which is a limitation of our research. Some studies have done biomicroscopy, especially in the recent literature. Conjunctival cytology may find eosinophils, basophils, as well as mast cells, while it will receive negative results inevitably.

On the other hand, we also take the tolerability and acceptance of children and guardians into consideration. In particular, the subjects are 5 to 10 years old, which makes it inevitable for them to have fears.

Among the 80-patient case study we conducted, our conclusion was relatively limited to the drug use of children; besides, the compliance of children is usually poor. It confirmed that olopatadine, edemastine, and LE were equally effective only in a small sample of children. As far as we all know, this is the first time in the comparison of three drugs, so it is still necessary for a long-term observation in a further large sample with anti-allergic drugs, and taking the adults as the subjects should be performed in the further clinical studies to certificate and validate this research.

**Conclusion**

In summary, the efficacy of olopatadine hydrochloride 0.1%, edemastine difumarate 0.05%, and LE suspension 0.5% was equal, and olopatadine hydrochloride 0.1%, edemastine difumarate 0.05%, and LE suspension 0.5% were more effective than vehicle. We expect the present study will be beneficial to clinical research and will be illuminating for ophthalmologists when selecting an appropriate ophthalmic solution in SAC.

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