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Research Article
Comparing Efficacy and Safety of Olopatadine and Emedastine in Patients with Allergic Conjunctivitis

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Abstract

Background and Objective: Anti-histamine and anti-inflammatory agents are used in treatment of allergic conjunctivitis. The objective of the study was to compare efficacy and safety of emedastine with olopatadine in Chinese allergic conjunctivitis patients. **Materials and Methods:** Total, 2,745 allergic conjunctivitis affected eyes were subjected to simple randomization. Patients received normal saline (VG group; n = 915), 0.2% olopatadine (OG group; n = 915) or emedastine (EG group; n = 915) in affected eyes. Interventions run for 15 days. The signs, symptoms and treatment-emergent adverse-effects were evaluated. **Results:** Olopatadine and emedastine were effective and safe in allergic conjunctivitis. In the morning, patients had the same satisfaction for the relief of symptoms for olopatadine and emedastine (4.32±0.25 vs. 4.29±0.38, p = 0.051). In the evening, patients had a higher satisfaction for the relief of symptoms for emedastine treatment than olopatadine treatment (4.12±0.11 vs. 2.14±0.11, p<0.0001). About 35% patients from OG group and 60% patients from the EG group have preferred their next prescription with the same treatment. Olopatadine was effective in all types of allergic conjunctivitis and emedastine was effective in seasonal and perennial allergic conjunctivitis only. For OG group, pharyngitis and for EG group, increased heart rates were reported as adverse effects. **Conclusion:** Olopatadine recommended in all types of conjunctivitis and emedastine recommended in seasonal and perennial allergic conjunctivitis only.

Key words: Allergic conjunctivitis, anti-inflammatory agents, anti-histamine, emedastine, olopatadine

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The conjunctiva is continuously faced entering of several of airborne antigens, which causes inflammation of it, called as allergic conjunctivitis[1]. It is classified as atopic keratoconjunctivitis, seasonal allergic conjunctivitis, vernal keratoconjunctivitis and perennial allergic conjunctivitis. Among this seasonal allergic conjunctivitis and perennial allergic conjunctivitis are the most frequently occurred manifestations[2]. Seasonal allergic conjunctivitis is acute or subacute manifestation characterized by ocular itching, dry eye, burning eye, redness of conjunctiva and pain in the eye[3]. Signs and symptoms of allergic conjunctivitis may decrease the quality of life and the productivity of an individual[3,4]. Conjunctival isolates are resistant to several antibiotics[5]. Anti-histamine and anti-inflammatory agents are used in treatment of allergic conjunctivitis[6].

Olopatadine is anti-histaminic and topical anti-allergic agent with mast cell-stabilizing (H-1 antagonist) properties provides rapid and long-lasting relief in allergic conjunctivitis. Olopatadine may perform better if it were used twice daily but its twice-daily dosing is not recommended[7]. Emedastine is benzimidazole derivative[8] and H-1 antagonist[9]. Emedastine is superior to antazoline and pheniramine[10] but required minimum twice daily administration for better effects.

In past, olopatadine is compared with emedastine in seasonal allergic conjunctivitis in a small-scale pilot study in adults[8] and children[9]. However, there is no study available with a large population to compare olopatadine with emedastine with all age group and all types of allergic conjunctivitis.

The objective of the study was to compare efficacy and safety of twice-daily 0.5 mg mL^{-1} emedastine difumarate with 0.222% olopatadine hydrochloride in all age group (Patients, 3 years and older and younger than 65 years) and all types (atopic keratoconjunctivitis, seasonal allergic conjunctivitis, vernal keratoconjunctivitis and perennial allergic conjunctivitis) of Chinese allergic conjunctivitis patients.

MATERIALS AND METHODS

Drugs and reagents: About 0.222% olopatadine hydrochloride (equivalent 0.2% olopatadine) ophthalmic solution (PATADAY™) and 0.5 mg mL^{-1} emedastine difumarate eye drops (EMADINE) were purchased from Alcon Laboratories, Inc., USA. Normal saline eye drops were purchased from Martindale Pharma., UK. Levobupivacaine (Chirocaine) and Papanicolaou were purchased from Abbott Laboratories Trading (Shanghai) Co., Ltd, Shanghai, China.

Ethical approval and consent to participate: The study had been registered in the Research Registry, UID No. research registry 4483 dated 15 January, 2017 (www.researchregistry.com). The protocol (GPH/GMU/CL/16/17 dated 11 January, 2017) of the study had been approved by the Guizhou provincial Hospital review board. An informed consent form had been signed by the enrolled patients regarding interventions, pathology and publications of the study in all formats (hard and/or electronics) including patient's personal information and/or image(s) by patients or their relatives. The study had adhered to the Good clinical practice of China[11], the consolidated standards of reporting trials (CONSORT) guidelines and declaration of Helsinki (V2008).

Inclusion criteria: Patients, 3 years and older and younger than 65 years with papilla in lower and upper palpebral, itching in eye(s), blinking of eye(s), conjunctival edema and/or sensation of foreign body in eye(s) available at outpatient setting of the Guizhou provincial Hospital, Guiyang, China and the referring hospitals from 17 January, 2017 to 2 July, 2018 were subjected to skin prick test[12]. The patients with positive skin prick test were included in the trial.

Exclusion criteria: Patients who refused to sign an informed consent form, younger than 3 years, older than 65 years and negative skin prick test were excluded from the trial. Patients who wore contact lens and intraocular pressure greater than 21 mm Hg in the subjected eye were excluded from the study. Patients who used anti-allergic medication (the history of 1 month) and on the treatment of any drug which causes eye disease(s) were excluded from the study. Pregnant and lactating females were excluded from the trial.

The demographic characteristics of enrolled patients are reported in Table 1.

Design of the study: A total of 2,745 affected eyes were subjected to simple randomization (1:1:1 ratio). Randomization was performed by the pre-filled envelope and maintained blind throughout the study by the Guizhou provincial Hospital, Guiyang, China itself. The sample size was calculated by PASS 16.0.3, NCSS, LLC, Utah, USA and found

Table 1: Demographic characteristics of enrolled patients

Characteristics	Groups			
Intervention	VG Normal saline n (%)	OG Olopatadine n (%)	EG Emedastine n (%)	Comparisons between groups p-value
Patients enrolled	801	795	805	
Eyes enrolled (sample size)	915	915	915	
Age (years)				
Minimum	5	5	5	0.06
Maximum	65	65	65	
Mean±SD	35.12±8.18	36.71±16.15	36.18±16.89	
Sex				
Male	548 (60)	529 (58)	569 (62)	0.16
Female	367 (40)	386 (42)	346 (38)	
Type of allergic conjunctivitis				
Keratoconjunctivitis	71 (8)	56 (6)	77 (8)	0.07
Seasonal allergic conjunctivitis	499 (54)	491(54)	446 (49)	
Vernal keratoconjunctivitis	19 (2)	29 (3)	28 (3)	
Perennial allergic conjunctivitis	326 (36)	339 (37)	364 (40)	
History				
Asthma	76 (8)	83 (9)	101 (11)	0.12
Rhinitis	172 (19)	191(21)	148 (16)	0.06

Continuous data were presented as Mean±SD and constant data were presented as number (percentage), One-way repeated measures ANOVA for continuous data and the chi-square independence test for constant data were used for statistical analysis, A $p<0.01$ were considered significant, All patients have China PR origin, all patients have acute allergic conjunctivitis

to be 915 for each group. The confidence level was 95% ($\alpha = 0.05$). The CONSORT flow diagram of the trial is presented in Fig. 1.

Intervention: The VG group (Vehicle group) patients received one drop of normal saline eye drops in affected eyes once a day. The OG group (olopatadine group) patients received once a day one drop of 0.222% olopatadine hydrochloride ophthalmic solution in affected eyes[13]. The EG group (emedastine group) patients received twice daily one drop of 0.5 mg mL^{-1} emedastine difumarate in affected eyes[14]. The interventions were continued for 15 days[8].

Signs and symptoms assessments of eyes: The signs and symptoms of eyes were assessed at the time of enrollment (baseline) at 8th day and after completion of interventions. Four-point scale method was adopted to code signs and symptoms. 0: Absent, 1: Mild, 2: Moderate, 3: Sever[8].

Conjunctival impression cytology assessments: The affected eyes were infiltrated with levobupivacaine injection in normal saline (Baxter, USA). The samples for impression cytology were collected with nitrocellulose acetate filter papers (NC-45, Sigma Aldrich, Shanghai, China). The collected samples were preserved in ethanol at 4°C and stained with Papanicolaou and checked under a microscope (Olympus, Beijing, China)[15]. Conjunctival impression cytology was performed at baseline and after completion of interventions.

Patients satisfaction were evaluated in morning and evening schedules during 15 days of interventions on the six-point scale method. 5: Extreme, 4: Good, 3: Good to moderate, 2: Moderate, 1: Mild, 0: Unsatisfied.

Treatment-emergent adverse effects: Information for adverse effects regarding applications of eye drops and the drugs themselves were gathered during a follow-up period of 3 months[1]. The effects were considered as treatment-emergent adverse effects as they are reported in the Medical Dictionary for Regulatory Activities[16].

Statistical analysis: InStat (version Window), GraphPad Software, IL, USA was used for statistical analysis. One-way analysis of variance (ANOVA) following Tukey-Kramer Multiple Comparisons Test (considering critical value $q>3.314$ as significant)[17] was used for continuous data. The chi-square independence test was used for constant data[8]. Results were considered significant 95% of confidence level per protocol method of analysis was adopted.

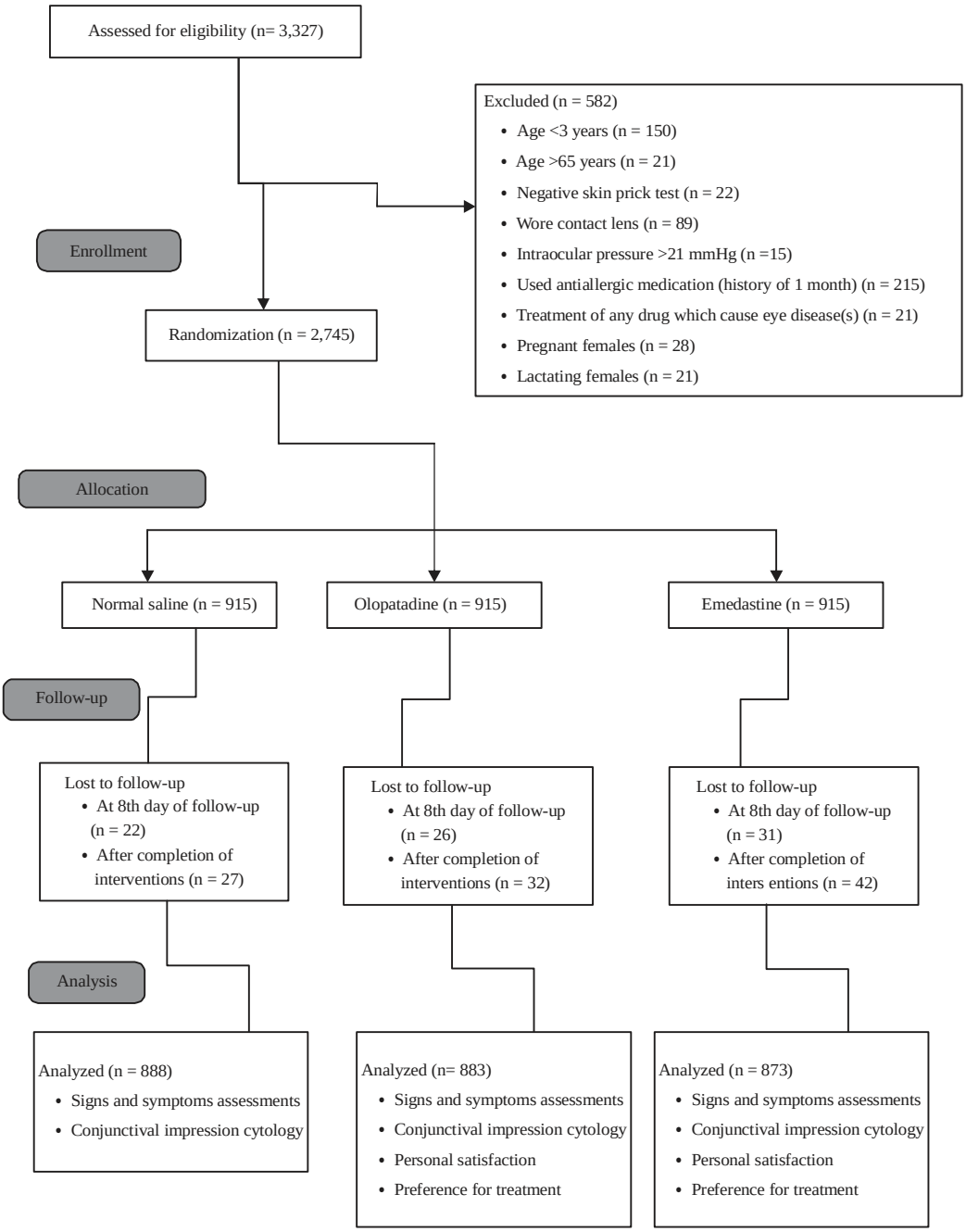

Fig. 1: CONSORT flow diagram of the study, $\alpha = 0.05$

RESULTS

About 22, 26 and 31 affected eyes from VG, OG and EG groups were lost for evaluation on at 8th day of follow-up and 27, 32 and 42 eyes from VG, OG and EG groups were lost for evaluation after completion of interventions.

Respect to normal saline, after 15 days of interventions, 0.2% olopatadine and 0.5 mg mL^{-1} emedastine difumarate were effective in allergic conjunctivitis.

In the morning, patients had the same satisfaction for the relief of symptoms for both treatments (4.32 ± 0.25 vs. 4.29 ± 0.38, $p = 0.051$). In the evening, patients had a higher satisfaction for the relief of symptoms for emedastine treatment than olopatadine treatment (4.12 ± 0.11 vs. 2.14 ± 0.11, $p<0.0001$, Fig. 2).

There were no significant differences for pathological grades of conjunctival impression cytology assessments between before and after interventions in all the treatment

Table 2: Conjunctival impression cytology assessments

	Groups								
	VG			OG			EG		
Intervention	Normal saline			Olopatadine			Emedastine		
Level	BL	EL		BL	EL		BL	EL	
	n (%)	n (%)	*p-value	n (%)	n (%)	*p-value	n (%)	n (%)	*p-value
Eyes enrolled (sample size)	915	888		915	883		915	873	
Pathological grading									
1	215(23)	235(26)	0.34	423(46)	380(44)	0.17	369(40)	341(39)	0.86
2	314(34)	297(34)		324(35)	311(35)		251(27)	239(27)	
3	386(43)	356(40)		168(19)	192(21)		295(33)	290(34)	

Grading according to the density of the goblet cells, BL: Baseline, EL: After completion of interventions, data were presented as number (percentage), *p-value between BL and EL, chi-square independence test was used for statistical analysis, A p<0.05 were considered significant, 1: Mild, 2: Moderate, 3: Severe

Table 3: Analysis of the effect of interventions according to types of allergic conjunctivitis

	Groups								
	VG			OG			EG		
Level	BL	EL		BL	EL		BL	EL	
	n (%)	n (%)	*p-value	n (%)	n (%)	*p-value	n (%)	n (%)	*p-value
Eyes enrolled (sample size)	915	888		915	883		915	873	
Types of allergic conjunctivitis									
Keratoconjunctivitis	71(8)	71(8)	N/A	56(6)	15(2)	<0.0001	77(8)	72(8)	0.07
Seasonal allergic conjunctivitis	499(54)	473(53)	0.62	491(54)	25(3)	<0.0001	446(49)	55(6)	<0.0001
Vernal keratoconjunctivitis	19(2)	19(2)	N/A	29(3)	14(2)	<0.0001	28(3)	23(3)	0.07
Perennial allergic conjunctivitis	326(36)	325(37)	0.32	339(37)	55(6)	<0.0001	364(40)	65(7)	<0.0001
Total recovery from allergic conjunctivitis	0(0)	0(0)	N/A	0(0)	774(87)	<0.0001	0(0)	658(76)	<0.0001

BL: Baseline, EL: After completion of interventions, data were presented as number (percentage), chi-square independence test was used for statistical analysis, A p<0.05 were considered significant, *p-value between BL and EL, N/A: Not applicable

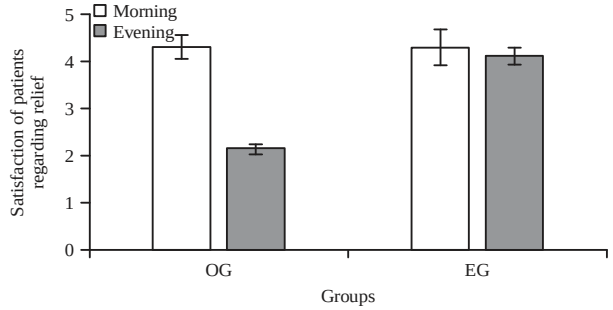

Fig. 2: Personal satisfaction evaluation of patients

Data were represented as mean of scale ±SD of them, Numbers of patients with an affected eye(s) evaluated for OG group and EG group were 780 and 779

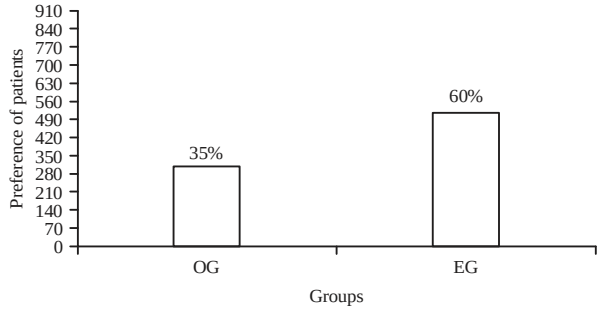

Fig. 3: Preference of patients for treatment after completion of 15 days of interventions

Data were represented as a percentage. Numbers of affected eyes evaluated for OG group and EG group were 883 and 873

groups ($p \leq 0.05$ for all, Table 2). About 0.2% olopatadine and 0.5 mg mL^{-1} emedastine difumarate after 15 days of interventions were safe to eyes.

Preference of patients was higher for emedastine treatment than olopatadine treatment (60 vs. 35%, Fig. 3).

After 15 days of interventions, 0.2% olopatadine was effective in all types of allergic conjunctivitis (Table 3). While, 0.5 mg mL^{-1} emedastine difumarate was effective in seasonal allergic conjunctivitis (Fig. 4a, b) and perennial allergic conjunctivitis only (Fig. 5a, b) but not effective in keratoconjunctivitis (Fig. 6a, b) and vernal keratoconjunctivitis (Fig. 7a, b).

For the OG group, pharyngitis, cold syndrome, blurred vision, total adverse effects and dry eyes and for EG group, the instillation-site abnormal sensation was reported as ocular treatment-emergent adverse effects (Table 4). For the OG group, nausea and rhinitis and for EG group, increased heart

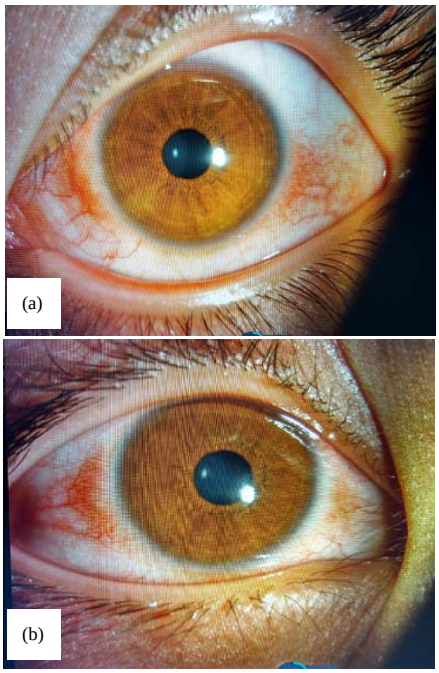

Fig. 4(a-b): Affected eye, (a) Seasonal allergic conjunctivitis at baseline and (b) Seasonal allergic conjunctivitis after completion of a twice daily one eye drops of 0.5 mg mL^{-1} emedastine difumarate for 15 days

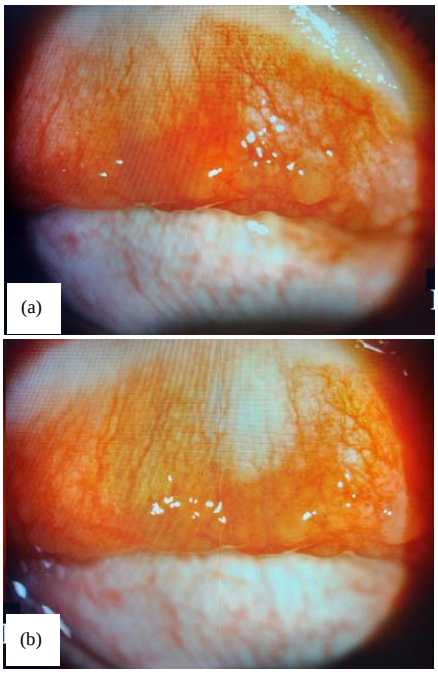

Fig. 5(a-b): Affected eye, (a) Perennial allergic conjunctivitis at baseline and (b) Perennial allergic conjunctivitis after completion of a twice daily one eye drops of 0.5 mg mL^{-1} emedastine difumarate for 15 days

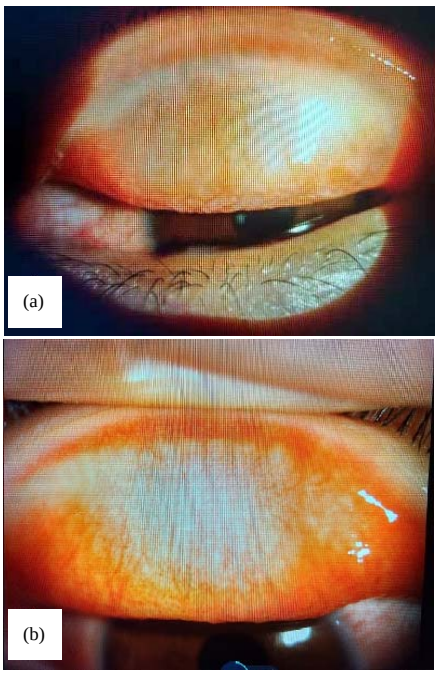

Fig. 6(a-b): Affected eye, (a) Keratoconjunctivitis at baseline and (b) Keratoconjunctivitis after completion of twice daily one eye drops of 0.5 mg mL^{-1} emedastine difumarate for 15 days

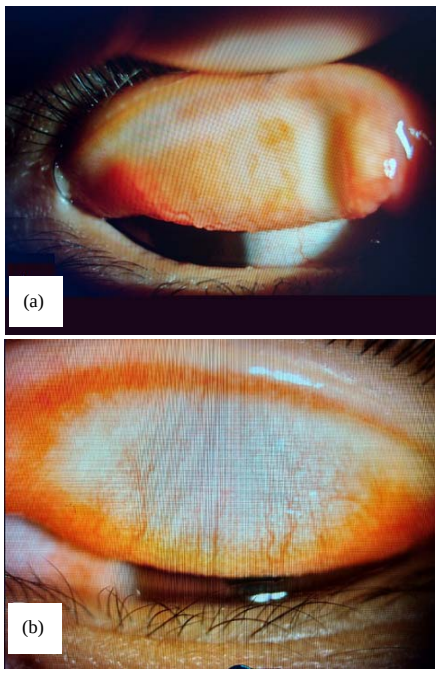

Fig. 7(a-b): Affected eye, (a) Vernal keratoconjunctivitis at baseline and (b) Vernal keratoconjunctivitis after completion of a twice daily one eye drops of 0.5 mg mL^{-1} emedastine difumarate for 15 days

Table 4: Ocular treatment-emergent adverse effects during the follow-up of 3 months

	Groups		
Adverse effects	OG	EG	
Intervention	Olopatadine	Emedastine	Comparisons between groups
	n (%)	n (%)	p-value
Eyes enrolled (sample size)	915	915	
Blurred vision	8(1)*	1(0.1)	0.045
Epidemic hemorrhagic conjunctivitis	5(0.5)	0(0)	0.073
Instillation-site abnormal sensation	1(0.1)	8(1)¥	0.045
Instillation-site stinging	0(0)	5(0.5)	0.07
Swollen eyelid	2(0.2)	2(0.2)	N/A
Cold syndrome	25(3)*	1(0.1)	<0.0001
Pharyngitis	21(2)*	1(0.1)	<0.0001
Dry eye	12(1)*	1(0.1)	0.005
Total adverse effects	74(9)*	19(2)	<0.0001

Data were presented as number (percentage), The chi-square independence test was used for statistical analysis, A p<0.05 were considered significant, N/A: Not applicable, *Significant olopatadine-emergent adverse effect, ¥Significant emedastine-emergent adverse effect

Table 5: Non-ocular treatment-emergent adverse effects during the follow-up of 3 months

	Groups		
Adverse effects	OG	EG	
Intervention	Olopatadine	Emedastine	Comparisons between groups
	n (%)	n (%)	p-value
Eyes enrolled (sample size)	915	915	
Back pain	2(0.2)	0(0)	0.48
Flue syndrome	3(0.3)	0(0)	0.25
Headache	5(0.5)	1(0.1)	0.22
Hyperemia	4(0.4)	0(0)	0.13
Cough	8(1)*	0(0)	0.013
Nausea	9(1)*	0(0)	0.008
Rhinitis	5(0.5)	0(0)	0.073
Sinusitis	2(0.2)	0(0)	0.48
Bad taste	1(0.1)	8(1)¥	0.045
Increased heart rate	0(0)	17(2)¥	<0.0001
Total adverse effects	39(4)	26(3)	0.13

Data were presented as number (percentage), The chi-square independence test was used for statistical analysis, A p<0.05 were considered significant, *Significant olopatadine-emergent adverse effect, ¥Significant emedastine-emergent adverse effect

Table 6: Cost of treatment

	Groups	
	OG	EG
Intervention	Olopatadine	Emedastine
Eyes enrolled (sample size)	915	915
Price/patient (¥)		
Cost of medicine	1150±15	820±30
Consultation charges	100±25	100±25
Total	1245±45	916±22

Data were presented as mean±SD

rates and bad taste were reported as non-ocular treatment-emergent adverse effects (Table 5). Overall, ocular treatment-emergent adverse effects and non-ocular treatment-emergent adverse effects were less than 10% and less than 5% in both treatments.

Patients of OG group had spent 1245±45 ¥/patient for treatment and those of EG group have spent 916±22 ¥/patient for treatment (Table 6).

DISCUSSION

A trial performed with once daily 0.2% olopatadine and twice daily 0.5 mg mL^{-1} emedastine difumarate in Chinese patients with allergic conjunctivitis. Several pharmaceutical agents have been preferred to handle allergic conjunctivitis[6]. Patients are not fully satisfied with over-the-counter allergic conjunctivitis relief drugs[7]. Epinastine[18] and ketotifen[19] are inferior to olopatadine in allergic conjunctivitis. Epinastine[20] and levocabastine[7] had favorable effects on ocular itching and hyperemia than allergic conjunctivitis. Loteprednol is required to administered four-times in a day[1]. Therefore, there are higher chances of the swollen eyelid and instillation-site abnormal sensation than olopatadine and emedastine[9]. About 0.77% olopatadine hydrochloride (equivalent 0.7% olopatadine) brand was not freely available in China PR at the time of the

study. With respect to efficacy and treatment-mergent adverse effects, the researchers justified the selection of medicinal agents for the trial.

With respect to normal saline, after 15 days of treatment, once-daily 0.2% olopatadine and twice daily 0.5 mg mL^{-1} emedastine difumarate were effective, safe and well tolerated in allergic conjunctivitis. Olopatadine blocks binding of the free histamine to receptors (antihistaminic) and prevents further release of proinflammatory mediators from the mast cells (H-1 antagonist)[3]. Emedastine is also mast cell-stabilizer[9]. The results of the trial were in line with the available studies[1,7-9,15,18,20-23]. With respect to results of signs and symptoms of patients reported during the study, olopatadine and emedastine both are good options for allergic conjunctivitis than over-the-counter drugs.

In the morning, patients' satisfaction for the relief of symptoms for olopatadine and emedastine were the same ($p = 0.051$) but in the evening, patients' satisfaction for emedastine was higher than olopatadine ($p<0.0001$). The results of the study were in line with an available study[7]. The possible reason for this event that olopatadine provides full relief from the signs and symptom in allergic conjunctivitis over the duration of 16 h in the day[21,23]. Therefore, olopatadine eye drops performs better at the time of administration.

According to the effect and irrespective to the cost, 35% patients from OG group and 60% patients from EG group have preferred their next prescription for the treatment of allergic conjunctivitis to be written with once daily olopatadine and twice daily emedastine respectively. The results of the study were in line with an available study[7] but were not in line with general patient preference and dosing frequency relationship[24]. In allergic conjunctivitis, patients will choose a twice-daily option for medication.

The trial reported that olopatadine was effective in all types of allergic conjunctivitis but emedastine was effective in seasonal and perennial allergic conjunctivitis only. The best of the researchers' knowledge, this was first ever analysis of the efficacy of emedastine according to types of allergic conjunctivitis. Olopatadine is an effective treatment for ocular itching related to all types of allergic conjunctivitis[13]. Emedastine is effective in seasonal allergic conjunctivitis[8,10,14]. The trial recommended olopatadine only in keratoconjunctivitis and vernal keratoconjunctivitis.

In the limitations of the study, for examples, once daily 0.2% olopatadine and twice a day 0.5 mg mL^{-1} emedastine difumarate were used in the trial. Both treatment drugs have different concentrations and different dosage regimens. Lower concentrations of emedastine might be responsible for its less effect in conjunctivitis. A further trial is recommended with the same concentration and the same dosage regimen. Although 0.7% olopatadine is considered as the reference standard for rapid and prolonged action in allergic conjunctivitis patients for 24 h protection in a day[22], the study was not performed using the reference standard. Patients were enrolled as per skin prick test. However, in seasonal allergic conjunctivitis skin prick test is sometimes found to be negative[25]. A further trial is required for patients with negative skin prick test or the other exact test like Schirmer's strip test[26] is required to rule out allergic conjunctivitis before enrollment.

CONCLUSION

Once-daily olopatadine performs better at the time of administration. Patients will choose a better treatment option than compliance option in allergic conjunctivitis. Olopatadine recommended in all types of conjunctivitis and emedastine recommended in seasonal and perennial allergic conjunctivitis only.

SIGNIFICANCE STATEMENT

A double-blind, vehicle-controlled trial for all types of conjunctivitis on a large population of Chinese patients concluded that olopatadine recommended in all types of conjunctivitis and emedastine recommended in seasonal and perennial allergic conjunctivitis only. The finding will help Ophthalmologists to uncover the critical areas of all type's allergic conjunctivitis in all age group of patients that many researchers are not able to explore.

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