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Original Research Article

Effect of co-administration of pranoprofen/emedastine difumarate eye drops on efficacy, inflammatory factors, tear film stability and immune function in children with allergic conjunctivitis

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Abstract

Purpose: *To investigate the clinical efficacy of pranoprofen eye drops when combined with emedastine difumarate eye drops for the treatment of children with allergic conjunctivitis.*
Methods: *A total of 96 children with allergic conjunctivitis admitted to Eye Hospital, China Academy of Chinese Medical Sciences from January 2020 to 2022 were enrolled in this study. They were divided into study group (treated with both pranoprofen eye drops and emedastine difumarate eye drops), and control group (treated with emedastine difumarate eye drops alone), with 48 children in each group. The control group was given emedastine fumarate eye drops 1 drop twice a day. The study group was given pranoprofen eye drops 2 drops 4 times a day in addition to the treatment administered to control group. Patients in both groups were observed and compared after one week of treatment. Efficacy, incidence of adverse reactions, symptom scores, inflammatory factors, tear film stability indicators and immune function indicators were assessed and recorded.*
Results: *Prior to treatment, there was no significant difference in symptom score, inflammatory factors, tear film stability indicators and immune function indicators between study and control groups. Although the above indicators improved in both groups after treatment, the study group showed significantly greater improvement than control group ($p < 0.05$). Overall clinical response rate in the study group (95.83 %) was higher than in the control group (77.08 %), while the incidence of adverse reaction in the study group (6.25 %) was lower than that of control group (27.08 %, $p < 0.05$).*
Conclusion: *Pranoprofen eye drops, when combined with emedastine difumarate eye drops for treatment of children with allergic conjunctivitis, is more effective than the use of emedastine difumarate eye drops alone. However, further clinical trials are required to validate the findings of this study prior to adoption of the combination treatment in clinical practice.*

Keywords: *Pranoprofen, Emedastine difumarate, Allergic conjunctivitis, Tear film stability, Immune function*

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INTRODUCTION

Allergic conjunctivitis is a common type of allergic disease, which is prevalent in clinical practice, and seasonal allergic conjunctivitis has a relatively high incidence [1,2]. Generally, the disease often appears in patients with asthma and allergic rhinitis. Surveys have revealed that

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the incidence of this disease is relatively high in more developed industrial countries, and it affects nearly 20 % of the world's population [3]. Moreover, due to increasing environmental pollution, and relatively low immunity in children, they are prone to attacks by pathogen, resulting in increasing incidence of this disease among this population. Hence, attention is gradually being given to this phenomenon [4]. For the treatment of allergic conjunctivitis, glucocorticoids and non-steroidal anti-inflammatory drugs as well as other therapies are commonly used [5].

Emedastine has a good therapeutic effect in children, but it is not a permanent cure. It prevents the expansion of ocular capillaries by blocking the binding of histamine and receptors, thus making the blood vessels smoother, in addition to the reduction of ocular itching. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce the production of prostaglandins by controlling the activation of cyclooxygenase (COX) in the body, preventing platelet aggregation as much as possible, and alleviating related symptoms in children. Pranoprofen eye drops are one of the NSAIDs with relatively good efficacy. Besides, the risk coefficients are low, and it has no adverse reactions [6]. Therefore, the aim of this study was to investigate the efficacy of co-administering of the two eye drop treatments in children with allergic conjunctivitis.

METHODS

Clinical profile of patients

A total of 96 children with allergic conjunctivitis admitted to Eye Hospital, China Academy of Chinese Medical Sciences from January 2020 to 2022 were divided into study and control groups, with 48 children in each group. There was no significant difference between both groups. All the procedures involving human participants were approved by the Ethics Committee of Eye Hospital, China Academy of Chinese Medical Sciences (approval no. YKEC-KT-2021-007-P002) and complied with the guidelines of the 1964 Helsinki Declaration and its later amendments for ethical research involving human subjects [7]. The consent of parents/guardians of the children was obtained for this study.

Inclusion criteria

(1) All patients who met the clinical diagnostic criteria for allergic conjunctivitis; (2) patients without related treatment and intervention before enrollment; (3) patients with good compliance; and (4) patients for which informed consent was given.

Exclusion criteria

Patients who were allergic to the relevant drugs; patients with other types of conjunctivitis; patients with other ophthalmic diseases.

Treatments

Control group

Patients in this group were given emedastine difumarate eye drops (s.a. Alcon-Couvreur n.v.; approval no. H20181192; strength (5 mL): 2.5 mg; 1 drop twice a day.

Study group

Patients in this group were given pranoprofen eye drops just like the control group (Senju Pharmaceutical Co. Ltd. Fukusaki Plant; approval no. H20130682; strength (5 mL): 5 mg; 2 drops 4 times a day.

The patients in both groups were treated for one week.

Evaluation of parameters/indicators

Clinical efficacy, adverse reactions, symptom scores, inflammatory factors, tear film stability indicators and immune function indicators were observed and compared.

Efficacy

Good response indicated that the symptoms in the children disappeared, and the bulbar conjunctiva returned to normal. *Moderate response* indicated that the symptoms of the child were significantly improved, but not completely disappeared, and the bulbar conjunctiva noticeably improved, but not completely normal; *No response* meant that the conditions did not reach the criteria for good response or moderate response.

Symptom score

Four dimensions were concluded (photophobia, foreign body sensation, lacrimation, eye itching). The score varied from 0 to 6; lower scores were synonymous with milder symptoms.

Biochemical indicators

Histamine (HA) and eosinophil cationic protein (ECP) levels were measured using enzyme-

linked immunosorbent assay (ELISA).

Tear film stability

Corneal fluorescein staining was utilized to determine fluorescein (FL) score (0-9), and a lower score indicated milder symptoms.

Immune function indicators

Immunoglobulin A (IgA), immunoglobulin G (IgG) and immunoglobulin E (IgE) were assessed using immunoturbidimetry.

Statistical analysis

Data were statistically processed using SPSS 23.0 software. Enumeration data are presented as n and %, while χ^2 test was used for comparison between the groups. Measurement data are expressed as mean ± standard deviation (SD), while t-test was applied for comparison of data between the groups. $P < 0.05$ indicated statistically significant differences.

Baseline patient data

There were no significant differences in clinical data between the two groups. The results are displayed in Table 1.

Symptom scores

Before treatment, there were no significant differences in all symptom scores between both groups. After treatment, all the symptom scores of the two groups decreased, but those of the study group were significantly lower than those of the control group ($p < 0.05$), as shown in Table 2 and Table 3.

Levels of inflammatory factors groups

Before treatment, there were no significant differences in the levels of inflammatory factors between the two groups. After treatment, however, the levels of inflammatory factors decreased in both groups, with the decrease more pronounced in the study group ($p < 0.05$). The results are shown in Table 4.

RESULTS

Table 1: Comparison of baseline patient data between both groups

Parameter/indicator		Study group (n=48)	Control group (n=48)	Statistical value	*P*-value
Mean age (years)		8.51±0.51	8.52±0.50	0.097	0.9229
Mean disease duration (days)		10.33±0.95	10.35±0.86	0.1081	0.9141
Gender (n, %)	*Male*	30	31	0.0450	0.8321
	Female	18	17		
Disease classification (n, %)	*Type I*	28	29	0.0432	0.8354
	Type II	20	19		
Severity (n, %)	*Mild*	25	26	0.0519	0.9744
	Moderate	16	15		
	Severe	7	7		
History of premature delivery (n, %)	*Yes*	12	11	0.0572	0.8110
	No	36	37		
History of cesarean section (n, %)	*Yes*	16	17	0.0462	0.8299
	No	32	31		
History of allergic rhinitis (n, %)	*Yes*	17	18	0.0450	0.8321
	No	31	30		
Adequate sleep (n, %)	*Yes*	25	26	0.0418	0.8379
	No	23	22		
First born or not (n, %)	*Yes*	32	33	0.0476	0.8272
	No	16	15		
Household registration (n, %)	*Nonlocal*	1	2	0.3441	0.5575

Table 2: Comparison of photophobia and foreign body sentation scores between both groups (mean ± SD, n = 48)

Group	Photophobia		t value	*P*-value	Foreign body sensation		t value	*P*-value
	Pre-treatment	*Post-treatment*			*Pre-treatment*	*Post-treatment*		
Study	3.63±0.49	1.15±0.41	26.893	0.000	3.96±0.54	1.13±0.49	26.889	0.000
Control	3.67±0.48	1.88±0.44	19.045	0.000	3.98±0.48	2.30±0.51	16.619	0.000
t value	0.404	8.4095	-	-	0.1918	11.4613	-	-
P-value	0.6871	0.0000	-	-	0.8483	0.0000	-	-

Table 3: Comparison of lacrimation and eye itching scores between both groups (mean ± SD, n = 48)

Group	Lacrimation		t value	*P*-value	Eye itching		t value	*P*-value
	Pre-treatment	*Post-treatment*			*Pre-treatment*	*Post-treatment*		
Study	3.89±0.33	1.04±0.51	32.5052	0.000	3.50±0.50	1.13±0.49	23.455	0.000
Control	3.90±0.37	2.15±0.46	20.538	0.000	3.52±0.50	2.23±0.42	13.687	0.000
t value	0.1397	11.1972	-	-	0.196	11.8088	-	-
P-value	0.8892	0.0000	-	-	0.8451	0.0000	-	-

Table 4: Comparison of levels of inflammatory factors between both groups (mean ± SD, n = 48)

Group	HA (μg/L)		t-value	*P*-value	ECP (μg/L)		t-value	*P*-value
	Pre-treatment	*Post-treatment*			*Pre-treatment*	*Post-treatment*		
Study	194.35±19.06	30.25±3.16	58.8462	0.0000	12.75±1.36	2.04±0.24	53.7294	0.0000
Control	195.06±18.95	64.35±6.35	45.3119	0.0000	13.09±1.29	7.16±0.79	27.1599	0.0000
t-value	0.183	33.3086	—	—	1.2567	42.9629	—	—
P-value	0.8552	0.0000	—	—	0.2120	0.0000	—	—

Table 5: Comparison of tear film stability between both groups (mean ± SD, n = 48)

Group	BUT (s)		t-value	*P*-value	FL (point)		t-value	*P*-value
	Pre-treatment	*Post-treatment*			*Pre-treatment*	*Post-treatment*		
Study	3.56±0.50	11.56±1.53	34.4338	0.0000	7.96±0.74	2.15±0.50	45.0717	0.0000
Control	3.58±0.50	6.25±0.64	22.7767	0.0000	7.98±0.67	6.08±0.65	14.1015	0.0000
t-value	0.196	22.1824	-	-	0.1388	33.2022	-	-
P-value	0.8451	0.0000	-	-	0.8899	0.0000	-	-

Note: BUT: tear break-up time; FL: fluorescein

Tear film stability

There was no significant difference in tear film stability between the two groups prior to treatment but this indicator improved in both groups, after treatment, with significantly greater improvement in the study group ($p < 0.05$), as shown in Table 5.

Immune function

Prior to treatment, immune function indicators were not significantly different between both groups but reduced after treatment. The reduction was, however, greater in the study group than in the control group ($p < 0.05$), as Table 6 shows.

Clinical efficacy

The overall response rate (ORR) in the study group was 95.83 %, which is significantly higher than 77.08 % in the control group ($p < 0.05$). The results are shown in Table 7.

Incidence of adverse reactions

The incidence of adverse reaction in the study group was 6.25 %, which is significantly lower than 27.08 % in the control group ($p < 0.05$). The results are displayed in Table 8.

DISCUSSION

Previous reports show that allergic conjunctivitis results from the excessive secretion of inflammatory cytokines that damage the conjunctival goblet cells and mucus layer, making the tear film more unstable [8]. At the same time, there is some close association between this disease and dry eye. The defensive ability of the ocular surface in children is reduced due to the incidence of dry eye, followed by increasingly severe allergic conditions [9].

Table 6: Comparison of immune function between both groups (mean ± SD, n = 48)

Group	IgA (g/L)		t-value	*P*-value	IgG (g/L)		t-value	*P*-value	IgE (mg/L)		t value	*P*-value
	Pre-treatment	***Post-treatment***			***Pre-treatment***	***Post-treatment***			***Pre-treatment***	***Post-treatment***		
Study	1.37±0.16	0.67±0.11	24.9774	0.0000	12.74±1.24	9.01±0.64	18.5193	0.0000	0.97±0.21	0.61±0.11	10.521	0.0000
Control	1.35±0.17	0.97±0.14	11.9546	0.0000	12.69±1.21	10.69±1.04	8.6845	0.0000	0.98±0.18	0.87±0.15	3.2526	0.0016
t-value	0.5935	11.6738	—	—	0.1999	6013.8756	—	—	0.2505	9.684	—	—
P-value	0.5542	0.0000	—	—	0.8420	0.0000	—	—	0.8028	0.0000	—	—

Table 7: Comparison of clinical efficacy between both groups (n, %)

Group	N	Good response	Moderate response	No response	Overall response
Study	48	31，64.58	15，31.25	2，4.17	46，95.83
Control	48	25，52.08	12，25.00	11，22.92	37，77.08
X^2					7.2067
P-value					0.0073

Table 8: Comparison of adverse reactions between both groups (n, %)

Group	N	Lacrimation	Irritation	Eyelid oedema	Total adverse reactions
Study	48	2，4.17	1，2.08	0，0.00	3，6.25
Control	48	6，12.50	5，10.42	2，4.17	13，27.08
X^2 value					7.5000
P-value					0.0062

As a propionic acid derivative, pranoprofen eye drops has a good inhibitory effect on the conversion of arachidonic acid to prostaglandins, and reduces the production of prostaglandins. Besides, it has a certain control effect on eosinophil chemotaxis, so that allergic reactions are prevented and IgE content in the body is reduced. However, the effect is similar to that of emedastine difumarate eye drops and ketotifen, alleviating ocular congestion and itching in patients [10]. In this study, the combination of these two drugs has achieved good results in the clinical treatment of allergic conjunctivitis. As shown in the results, the combined drug therapy exhibited some comparative advantages over the single therapy in terms of response rate, adverse reaction control and symptom improvement.

It has been shown that pranoprofen exerted an effect in alleviating ocular inflammation in patients by chemotaxis of eosinophils and control of prostaglandin secretion, which effectively alleviated inflammation and pain [11]. It also relieves conjunctival congestion and lacrimation, although in clinical trials of non-steroidal anti-inflammatory drugs, it did not trigger infection or increase intraocular pressure. Emedastine difumarate eye drops is a selective H1 receptor antagonist that inhibits the binding of histamine to H1 receptors[11]. The results of this study revealed that the combined treatment ameliorated the symptoms of photophobia, foreign body sensation, lacrimation, and eye itching in the patients, thus further confirming the previous report. In clinical practice, allergic reactions are often detected by histamine (HA) and eosinophil cationic protein (ECP) indicators. It has been reported that the degranulation of mast cells promotes a large increases in these two indicators [12]. Eosinophils play a critical role in allergic conjunctivitis and the secretion of the toxic protein, ECP [13]. Pranoprofen alleviates inflammation by infiltrating the lesions by controlling this cell and preventing inflammatory cytokines from stimulating the lesions [14]. As a selective histamine H1 receptor blocker, emeastine reduces the penetration of conjunctival vascular by controlling eosinophil chemotaxis, thereby exerting anti-inflammatory effect. The results of this study showed that the combined treatment was more effective in controlling the inflammatory response of patients. This result is consistent with other studies [15].

Pranoprofen functions in stabilizing cell membranes, and alleviates tissue edema and the ocular irritation caused by nerve sensitization [16]. Emedastine relieves inflammation by reducing phosphoinositide (PI) hydrolysis, thereby reducing inflammatory cytokines such as IL-6 produced by epithelial cells. Moreover, these agents exerted a concentration-dependent effect on histamine-induced conjunctival vascular permeability, and decreased cell adhesion molecule-1 (CAM) content by blocking histamine receptors [17]. In the present study, the tear film stability index of patients in the study group was also better than in the control group. Hence, co-administration of pranoprofen and emedastine difumarate eye drops effectively maintained tear film stability. Mast cells play an essential role in the development of this disease, and are activated by facilitating IgE-binding antigens to accelerate the secretion of several inflammatory mediators such as kinins and histamine, strengthen the vascular permeability of the conjunctiva, and increase vasodilatation. Ocular surface tissue containing IL-5 and IL-4 and other inflammatory mediators easily lead to eye itching and edema. Given that immunoglobulin is unable to pass the epithelial cell space of the conjunctiva, less immunoglobulin is presented. IgG digests pathogens by accelerating phagocytosis via macrophages. IgA protects the corneal surface, while IgE regulates the antibodies of allergic diseases [18]. Both emedastine difumarate eye drops and pranoprofen contain active ingredients that enhance immune function by ameliorating clinical symptoms such as ocular redness and swelling in children with allergic conjunctivitis [18]. The major cause of the disease is allergic reactions transduced by IgE antibody vectors. The findings of this study indicate that the combined treatment resulted in enhanced immune functions in patients.

Limitations of this study

The patients involved in this study were all young children drawn from one health facility. Thus, the sample size was small, and the subsequent follow-up time of patients was relatively short.

CONCLUSION

The co-application of pranoprofen and emedastine difumarate eye drops in the treatment of children with allergic conjunctivitis alleviates inflammation in the patients, maintains tear film stability, enhances immune functions in the eyes of the patients, and leads to improved efficacy. Nonetheless, further clinical studies are

required prior to adoption of this combined therapy in clinical practice.

DECLARATIONS

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Ethical approval

This work was approved by the Ethics Committee of Eye Hospital, China Academy of Chinese Medical Sciences (approval no. YKEC-KT-2021-007-P002).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Shasha Zhang and Leiyan Su designed the study and carried them out; Shasha Zhang, Leiyan Su, Zefeng Kang, Shoukang Zhang and Jing Wang supervised the data collection, analyzed as well as interpreted the data; and Shasha Zhang and Leiyan Su prepared the manuscript for publication and reviewed the draft of the manuscript. All authors read and approved this manuscript for publication.

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