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Original article

Loteprednol etabonate in the treatment of allergic conjunctivitis: a meta-analysis

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Abstract

Objective:

This meta-analysis was designed to assess the efficacy, as well as the safety of loteprednol etabonate (LE) ophthalmic suspension compared with placebo and other commonly used eye drops for treatment of allergic conjunctivitis.

Methods:

Comprehensive searches of randomized controlled trials were carried out in a database of Medline, Embase, and the Cochrane Library. Eight qualified studies were included. This study assessed the reduction from baseline in scores of cardinal signs and symptoms, proportion of patients with improvement of allergic signs and symptoms, and incidence of clinically significant intraocular pressure (IOP) elevation (IOP elevation ≥ 10 mmHg).

Results:

The results showed that topical LE was significantly superior to placebo in reduction from baseline in signs scores (standardized mean difference [SMD] = -0.48 ; 95% confidence interval [CI] = -0.65 to -0.32) and symptoms scores (weighted mean difference [WMD] = -0.51 ; 95% CI = -0.64 to -0.38) of allergic conjunctivitis, and as effective as olopatadine and fluorometholone acetate. Topical LE was associated with a higher improvement rate of signs (risk ratio [RR] = 1.53 ; 95% CI = 1.26 – 1.86 ; $I^2 = 57\%$) and symptoms (RR = 1.29 ; 95% CI = 1.15 – 1.46 ; $I^2 = 54\%$) than placebo and the positive control treatment. Clinically significant IOP elevation was more frequent in the group of LE than the group of control treatment (pooled odds ratio = 3.03 ; 95% CI = 1.04 – 8.80), which was affected by the response to corticosteroid of the individual patient and the wearing of contact lenses.

Conclusions:

Topical LE is effective in treating allergic conjunctivitis. However, it should be used with caution due to the higher incidence of IOP elevation compared with placebo and olopatadine. A large-scale trial would be required to confirm the effect of different concentrations of LE on IOP.

Introduction

Allergic conjunctivitis is a common disorder, which may affect 15–40% of the world population¹. Owing to the widespread use of contact lenses, genetic influence, increased industrialization, and environmental pollution, the prevalence of allergic conjunctivitis worldwide has increased over the past few decades^{2–4}.

Allergic conjunctivitis is an allergen-induced inflammatory response in the ocular surface¹. Based on clinical presentations, it is classified into five categories: seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis (GPC)⁵. Several pharmacologic eye drops have been applied to the management of allergic conjunctivitis, consisting of

anti-histamines, mast cell stabilizers, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunomodulatory agents⁶.

Meta-analyses results have shown that topical NSAIDs, topical cyclosporine, and sublingual immunotherapy were superior to placebo for treating allergic conjunctivitis⁷⁻⁹. Topical corticosteroids possess potent anti-inflammatory effects and are the main treatment for more severe forms or the acute phase of allergic conjunctivitis⁵. The limitation of the use of them arises from adverse reactions, such as increased intraocular pressure (IOP), glucocorticoid-induced glaucoma, cataract, and increased susceptibility to microbial infection¹⁰.

Loteprednol etabonate (LE) is a corticosteroid which differs structurally from ketone corticosteroids such as prednisolone in that the ketone at the carbon-20 position is replaced by a chloromethyl ester¹¹. Theoretically, this special structure makes topical LE safe in terms of IOP elevation¹¹. However, published randomized controlled trials (RCT) have reported controversy results about the IOP elevation incidence of topical LE in treatment of allergic conjunctivitis¹²⁻¹⁵. The purpose of this systematic review is to assess the safety, as well as the efficacy of topical LE, in management of allergic conjunctivitis.

Methods

Search strategy

We carried out comprehensive searches in Medline, Embase, and the Cochrane Controlled Trials Register using the terms 'loteprednol etabonate', 'loteprednol', 'allergic conjunctivitis', 'atopic conjunctivitis', 'vernal conjunctivitis', 'vernal keratoconjunctivitis', 'giant papillary conjunctivitis', 'seasonal allergic conjunctivitis', 'perennial allergic conjunctivitis', 'ocular allergy', and 'allergic eye disease'. We also went through the references of original articles and systematic reviews about allergic conjunctivitis to check if there were studies not yet recorded in the digital databases.

Trial selection and outcome measures

The criteria for clinical trials included in this meta-analysis were as follows: (1) study design: RCT; (2) population: both children and adults with allergic conjunctivitis, including SAC, PAC, VKC, AKC and GPC; (3) intervention: topical LE treatment; (4) comparison intervention: placebo or commonly used eye drops to treat allergic conjunctivitis; and (5) at least one of the following outcomes: signs severity score, symptoms severity score, the proportion of patients with improvement of allergic signs and symptoms, and occurrence of clinically significant IOP elevation. The criterion of clinically significant IOP elevation is an increase from baseline

to 10 mmHg (1.33 KPa) or more. We selected the improvement of cardinal signs (bulbar conjunctival injection or papillae) and symptoms (ocular itching) of allergic conjunctivitis for efficacy analysis, and the incidence of clinically significant IOP elevation for safety evaluation. Studies were excluded if these signs and symptoms were not well defined and graded or control eye drops were not used.

After completion of the searches, three authors (L.-Q.W., X.C., H.L.) worked independently to determine the eligible trials. If more than one published article studied the same population, the one that reported the latest results was included in this meta-analysis.

Data extraction

Three authors (L.-Q.W., X.C., H.L.) independently reviewed the full texts of included studies and performed the data extraction. Any disagreement on study or data was resolved by discussion among authors. We extracted the relevant data into pre-designed forms, including the authors names, publication date, trial design, location, number of participants, control treatment, participant age, sex, length of follow-up, topical LE concentration, duration of treatment, number of subjects that completed the study, and outcome variables. The extracted outcomes were reduction in signs and symptoms severity scores from baseline, the number of patients with improvement of signs and symptoms, and clinically significant IOP elevation. Standard deviation (SD) was obtained from the standard error (SE) of a mean by multiplying the square root of the sample size¹⁶. When the mean and SD of change from baseline in signs and symptoms severity scores was absent, they could be calculated based on the formulae in the *Cochrane Handbook for Systematic Reviews of Interventions*¹⁶ as follows:

$$\begin{aligned}\text{Mean}_{\text{change}} &= \text{Mean}_{\text{baseline}} - \text{Mean}_{\text{final}}, \\ \text{SD}_{\text{change}}^2 &= \text{SD}_{\text{change}}^2 + \text{SD}_{\text{final}}^2 - 2 \times 0.8 \times \text{SD}_{\text{baseline}} \\ &\quad \times \text{SD}_{\text{final}}.\end{aligned}$$

We interpolated outcome measures from figures if the numerical values were not reported in the texts.

Qualitative assessment

Three authors (L.-Q.W., X.C., H.L.) appraise independently the methodological quality of the studies enrolled. Risk of bias was classified as high, low, or unclear according to the Cochrane Risk of Bias Tool for RCTs¹⁶.

Statistical analysis

We analyzed the change from baseline in signs and symptoms scores as continuous variables, whereas the number of

patients with improvement of allergic signs and symptoms and with clinically significant IOP elevation were analysed as dichotomous variables. We used RevMan software version 5.2 (the Cochrane Collaboration, Oxford, UK) for meta-analysis. We used standardized mean difference (SMD) for reduction in signs scores, weighted mean difference (WMD) for change in symptoms scores, Mantel-Haenszel risk ratio (RR) for the proportions of patients with improvement of signs and symptoms, and Mantel-Haenszel odds ratio (OR) for incidence of clinically significant IOP elevation, with 95% confidence intervals (CIs). We analyzed statistical heterogeneity of the included studies using Cochrane Q-statistics chi-square test and I^2 statistic. If no heterogeneity was observed between studies, a fixed effects model was applied; otherwise, a random effects model was used. We constructed funnel plots to examine the potential publication bias.

Sensitivity analysis

Sensitivity analysis was conducted to examine the influence of methodologic features, comparison intervention, concentration of topical LE, and the type of allergic conjunctivitis on the results of this meta-analysis.

Results

A total of 195 records were searched. The flow of selecting eligible trials is shown in Figure 1. Eighty-two records were ruled out due to being irrelevant, not case-controlled, or improper article types (review, case report, abstract, or commentary). Subsequently, the full texts of nine studies were reviewed for eligibility, and one was excluded because it was based on the conjunctival provocation test model. Finally, eight RCTs were included in this meta-analysis.

Study characteristics

Eight clinical trials including a total of 1445 participants were qualified for inclusion. Seven hundred and twenty-four patients were in the LE group and 721 ones in the control group. In the control group, 552 subjects were treated with placebo, 149 with topical olopatadine, and 20 with topical fluorometholone acetate. Among these trials, six were conducted in the US, one in China, and one in Turkey. Four trials specifically included SAC patients^{12,17-19}, three enrolled GPC patients^{14,15,20}, and one contained VKC patients¹³. Six trials were multi-center RCTs. The characteristics of the eight studies are summarized in Table 1.

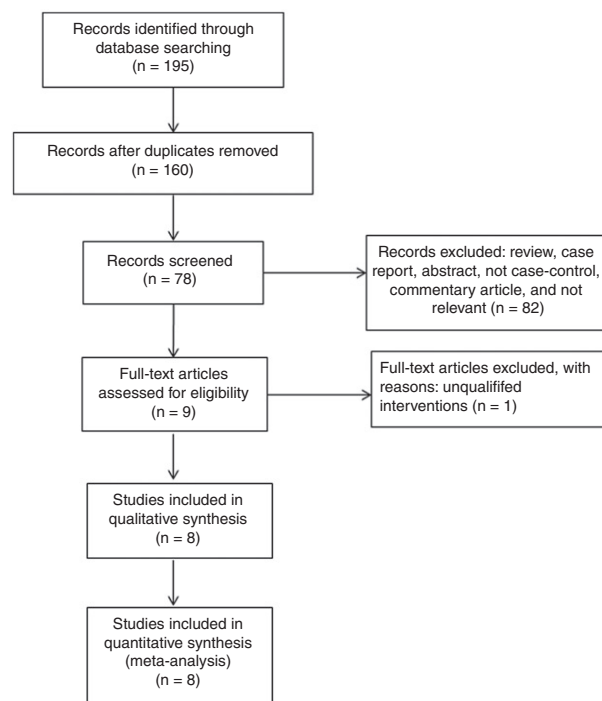


Figure 1. PRISMA flow diagram showing selection of studies during this meta-analysis.

Quality assessment

Table 2 shows the risk of bias results of the eight trials. For selection bias, three studies using a computer-generated randomization code/list and one referring to a random number list were evaluated as low risk. Seven studies provided information about the method of allocation concealment, and two of them^{14,20} adopting an open random allocation schedule (random numbers) were judged as high risk. For performance and detection biases, all except two studies were double-masked (subjects and outcome investigators). For attributing bias, all the studies were considered as low risk because the reasons for the subjects quitting the study were unlikely to affect the outcome. We could not comment on the selective reporting bias because we did not have access to the study protocols, but all outcomes described in respective methodologies were reported. Three studies were at high risk of other bias, because two trials^{14,20} contained participants known as 'corticosteroid responders' at baseline, and one¹⁵ allowed GPC patients to continue or discontinue contact lens determined at random.

Publication bias

The funnel plot of the proportion of patients with clinically significant IOP elevation was shown to be qualitatively symmetrical, indicating that there was no publication bias (Figure 2).

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Table 1. Characteristics of included trials.

Reference	Study design	Center	Location	Pts (n)	Control	Mean age, Yr (±SD)		Male/Female		FU (wk)	Conc. of LE	Regimen; duration	Completion of FU	
						LE	Control	LE	Control				LE	Control
Öner <i>et al.</i> ¹³	SB RCT	Single	Turkey	40	FA	21.85 (7.51)	22.05 (6.92)	15/5	14/6	4	0.5%	4 times/day; 4 wk	20/20	20/20
Gong <i>et al.</i> ¹⁷	SB RCT	Multi	China	300	Olopatadine	40.5 (14.01)	40.6 (12.85)	52/99	46/103	15 days	0.2%	4 times/day; 15 days	140/151	143/149
Shulman <i>et al.</i> ¹²	DB RCT	Multi	US	135	Placebo	39.2 (10.5)	38.2 (9.3)	31/36	31/37	6	0.2%	4 times/day; 6 wk	5/67	3/68
Dell <i>et al.</i> ¹⁸	DB RCT	Multi	US	133	Placebo	41	42	33/33	35/32	6	0.2%	4 times/day; 6 wk	8/66	8/67
Dell <i>et al.</i> ¹⁹	DB RCT	Multi	US	288	Placebo	42.1 (13.25)	41.8 (13.15)	22/123	29/114	7	0.5%	4 times/day; 6 wk	248/288	
Friedlaender and Howes ²⁰	DB RCT	Multi	US	219	Placebo	33.4 (11.48)	31.8 (8.390)	23/86	31/79	7	0.5%	4 times/day; 6 wk	85/109	90/110
Asbell and Howes ¹⁴	DB RCT	Multi	US	220	Placebo	34.1 (10.536)	33.1 (10.44)	28/83	25/84	7	0.5%	4 times/day; 6 wk	89/111	91/109
Bartlett <i>et al.</i> ¹⁵	DB RCT	Multi	US	110	Placebo	NR	NR	NR	NR	4	0.5%	4 times/day; 4 wk	55/55	55/55

SB, single blind; DB, double blind; RCT, randomized controlled trial; Pts, patients; FU, follow-up; LE, loteprednol etabonate; US, United States; wk, weeks; Yr, years; Conc., concentration; SD, standard deviation; FA, fluorometholone acetate; NR, not reported.

Outcome measures

Change from baseline in signs severity scores

Six trials reported the data about reduction in signs scores from baseline, and the outcomes are shown in Table 3. Topical LE was associated with a greater decrease in signs scores than control treatment. The pooled SMD was −0.85 (95% CI = −1.35 to −0.35; I^2 = 91%; Figure 3). Excluding the heterogeneous studies^{13,15,17} with high risk bias which were likely to influence the outcomes did not change the results, and no significant heterogeneity was found.

We divided the studies into two groups according to control treatment (placebo and positive control). Topical LE produced significantly greater reduction from baseline in signs scores than did placebo, and showed no significant difference compared to positive control treatment (topical olopatadine and fluorometholone acetate).

Then, we compared independent sub-groups of studies differing in the concentration of topical LE (0.2% and 0.5%). Both concentrations of topical LE were superior to control treatment in signs score reduction.

In addition, we divided studies into different sub-groups according to the type of allergic conjunctivitis (SAC, GPC, and VKC). The differences in signs scores reduction were all statistically significant, comparing topical LE with control treatment.

Finally, we stratified the trials by methodological characteristics (double blind and single blind). Topical LE showed a better therapeutic effect than control treatment in the double blind group, and a similar effect to control treatment in the single blind group.

Proportion of patients with improvement of allergic signs

We analyzed the proportion of patients with positive response, comparing topical LE with control treatment. Topical LE was associated with a higher improvement rate of signs than control treatment. The overall RR was 1.50 (95% CI = 1.35–1.68; I^2 = 57%; Figure 4). Statistically significant heterogeneity was detected. When the heterogeneous study was excluded¹⁷, no significant heterogeneity was found, and the difference between topical LE and control treatment was still statistically significant (p < 0.0001; Table 4).

We carried out sensitivity analysis and the results are shown in Table 4. Topical LE produced significantly greater improvement rate of ocular allergic signs than placebo and positive control treatment (topical olopatadine), respectively. Both topical 0.2% LE and 0.5% LE showed a higher response rate than the control treatment. For SAC and GPC, there was a statistically significant advantage for loteprednol.

Table 2. Risk of bias summary of included studies.

Reference	Randomization method	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Bartlett <i>et al.</i> ¹⁵	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Asbell and Howes ¹⁴	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Friedlaender and Howes ²⁰	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Dell <i>et al.</i> ¹⁹	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dell <i>et al.</i> ¹⁸	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Shulman <i>et al.</i> ¹²	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gong <i>et al.</i> ¹⁷	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Öner <i>et al.</i> ¹³	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk

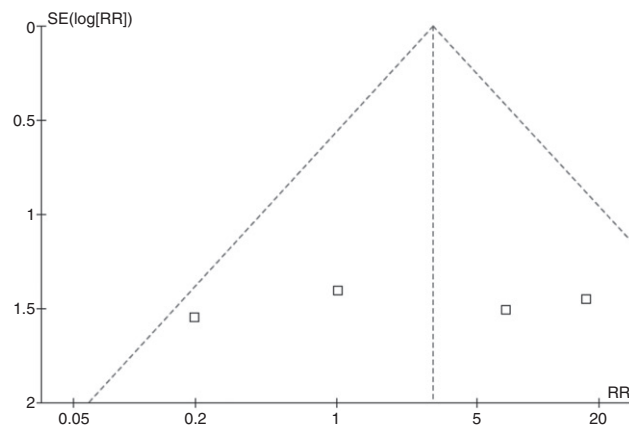


Figure 2. Funnel plot of the proportion of patients with clinically significant IOP elevation.

Table 3. Change from baseline in signs severity scores.

	No. of trials	LE <i>n</i>	Comparison intervention <i>n</i>	MD (95% CI)	Test for heterogeneity	Test for overall effect
All trials	6	451	457	-0.85 (-1.35, -0.35)	$p < 0.00001, I^2 = 91\%$	$p = 0.0009$
No heterogeneous	3	238	240	-0.48 (-0.67, -0.30)	$p = 0.63, I^2 = 0\%$	$p < 0.00001$
Placebo	4	293	295	-0.48 (-0.65, -0.32)	$p = 0.82, I^2 = 0\%$	$p < 0.00001$
Positive control	2	158	162	-3.78 (-10.61, 3.04)	$p < 0.00001, I^2 = 98\%$	$p = 0.28$
0.2%LE	3	267	272	-0.45 (-0.62, -0.28)	$p = 0.48, I^2 = 0\%$	$p < 0.00001$
0.5%LE	3	184	185	-2.11 (-3.57, -0.65)	$p < 0.00001, I^2 = 96\%$	$p = 0.005$
SAC	3	267	272	-0.45 (-0.62, -0.28)	$p = 0.48, I^2 = 0\%$	$p < 0.00001$
GPC	1	109	110	-0.40 (-0.67, -0.13)	Not applicable	$p = 0.003$
VKC	1	20	20	-7.33 (-9.13, -5.53)	Not applicable	$p < 0.00001$
Double blind	4	293	295	-0.48 (-0.65, -0.32)	$p = 0.82, I^2 = 0\%$	$p < 0.00001$
Single blind	2	158	162	-3.78 (-10.61, 3.04)	$p < 0.00001, I^2 = 98\%$	$p = 0.28$

The sensitivity analysis of methodologic characteristics showed no significant heterogeneity in these analyses, and the differences in positive response rate were all statistically significant.

Change from baseline in symptoms severity scores

The analysis results about change from baseline in ocular allergic symptoms, comparing topical LE and control treatment, were displayed in Figure 5 and Table 5. Topical LE significantly reduced the scores of cardinal symptoms of

allergic conjunctivitis compared to control treatment. The combined WMD was -0.66 (95% CI = -0.97 to -0.35; $I^2 = 89\%$; Figure 5). When the heterogeneous study was excluded^{13,17}, the difference between topical LE and control treatment was still statistically significant ($p < 0.0001$), and no significant heterogeneity was found.

Sensitivity analysis was carried out. All the differences were statistically significant, except for the results comparing topical LE and positive control treatment.

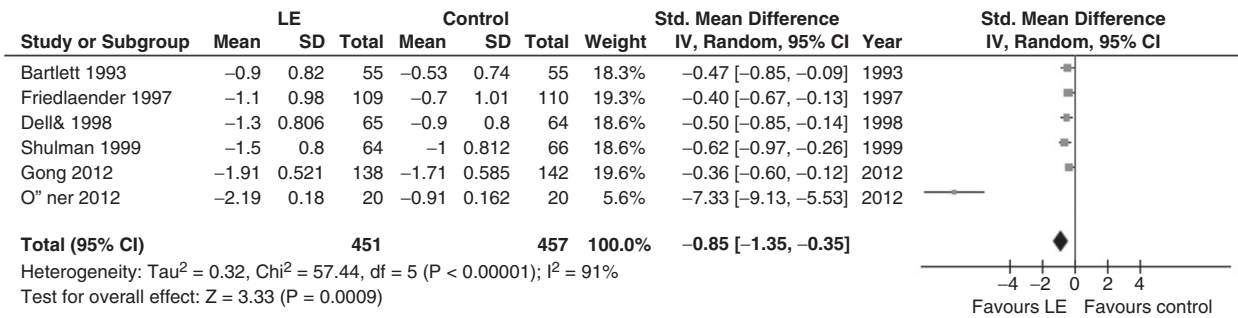


Figure 3. Graph showing the effect of topical LE vs control treatment on the reduction from baseline of allergic signs scores. Std. = standardized.

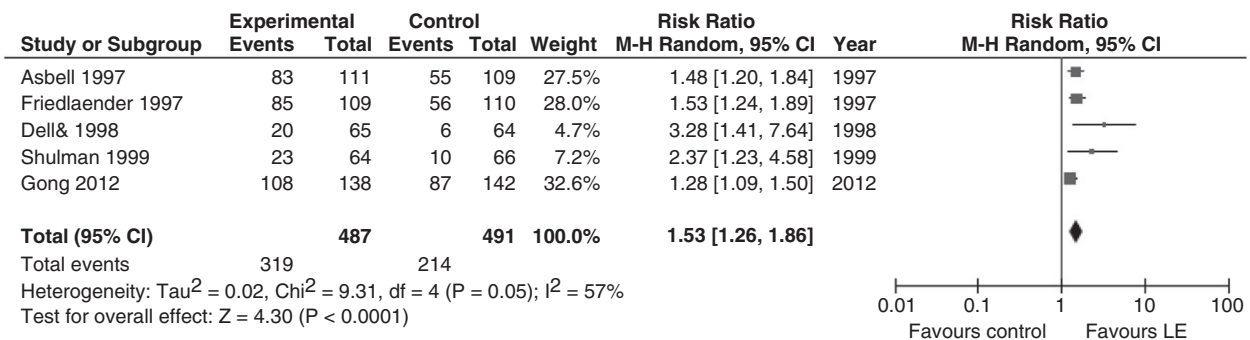


Figure 4. Graph showing the effect of topical LE vs control treatment on the proportion of patients with improvement of allergic signs.

Table 4. Proportion of patients with improvement of allergic signs.

	No. of trials	Crude rate		RR (95% CI)	Test for heterogeneity	Test for overall effect
		LE	Comparison intervention			
All trials	5	319/487	214/491	1.53 (1.26, 1.86)	$p = 0.05$, $I^2 = 57\%$	$p < 0.0001$
No heterogeneous	4	211/349	127/349	1.66 (1.32, 2.09)	$p = 0.15$, $I^2 = 43\%$	$p < 0.0001$
Placebo	4	211/349	127/349	1.66 (1.43, 1.93)	$p = 0.15$, $I^2 = 43\%$	$p < 0.00001$
Positive control	1	108/138	87/142	1.28 (1.09, 1.50)	Not applicable	$p = 0.002$
0.2%LE	3	151/267	103/272	1.98 (1.01, 3.89)	$p = 0.01$, $I^2 = 78\%$	$p = 0.05$
0.5%LE	2	168/220	111/219	1.51 (1.30, 1.75)	$p = 0.83$, $I^2 = 0\%$	$p < 0.00001$
SAC	3	151/267	103/272	1.98 (1.01, 3.89)	$p = 0.01$, $I^2 = 78\%$	$p = 0.05$
GPC	2	168/220	111/219	1.51 (1.30, 1.75)	$p = 0.83$, $I^2 = 0\%$	$p < 0.00001$
Double blind	4	211/349	127/349	1.66 (1.43, 1.93)	$p = 0.15$, $I^2 = 43\%$	$p < 0.00001$
Single blind	1	108/138	87/142	1.28 (1.09, 1.50)	Not applicable	$p = 0.002$
Allocation concealment	4	299/422	208/427	1.45 (1.24, 1.68)	$p = 0.17$, $I^2 = 40\%$	$p < 0.00001$
Unclear allocation concealment	1	20/65	6/64	3.28 (1.41, 7.64)	Not applicable	$p = 0.006$

Proportion of patients with improvement of allergic symptoms

There were five studies included in this analysis. The results about the proportion of patients with improvement of ocular allergic symptoms, comparing topical LE and control treatment, are shown in Figure 6 and Table 6. Improvement rate of allergic symptoms strongly favored topical LE over control treatment. Excluding the heterogeneous study¹⁷ did not change the results.

The sensitivity analysis was carried out to evaluate the influence of comparing intervention, concentration of topical LE, type of allergic conjunctivitis, and methodologic characteristics on the results of this meta-analysis. There were a numerically greater proportion of patients with positive response treated with topical LE, compared with control treatment, and the differences were all statistically significant (Table 6).

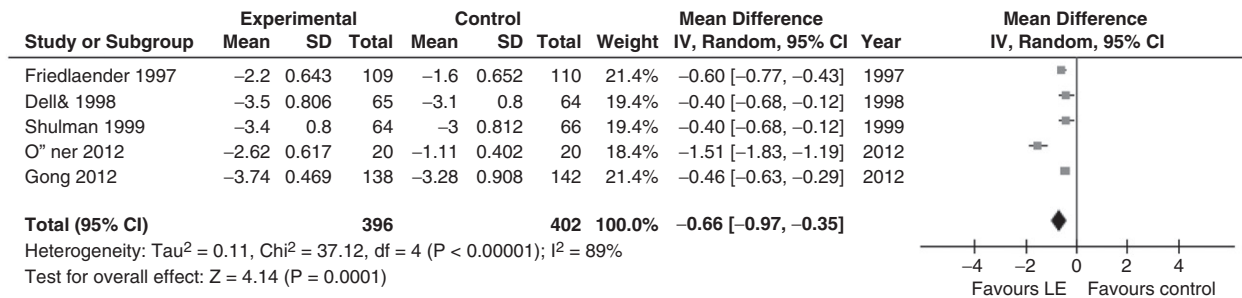


Figure 5. Graph showing the effect of topical LE vs control treatment on the reduction from baseline of allergic symptoms scores.

Table 5. Change from baseline in symptoms severity scores.

	No. of trials	LE, n	Comparison intervention, n	WMD (95% CI)	Test for heterogeneity	Test for overall effect
All trials	5	396	402	-0.66 (-0.97, -0.35)	$p < 0.00001$, $I^2 = 89\%$	$p < 0.0001$
No heterogeneous	3	238	240	-0.51 (-0.65, -0.37)	$p = 0.32$, $I^2 = 12\%$	$p < 0.00001$
Placebo	3	238	240	-0.51 (-0.64, -0.38)	$p = 0.32$, $I^2 = 12\%$	$p < 0.00001$
Positive control	2	158	162	-0.98 (-2.00, 0.05)	$p < 0.00001$, $I^2 = 97\%$	$p = 0.06$
0.2%LE	3	267	272	-0.43 (-0.56, -0.31)	$p = 0.90$, $I^2 = 0\%$	$p < 0.00001$
0.5%LE	2	129	130	-1.04 (-1.94, -0.15)	$p < 0.00001$, $I^2 = 96\%$	$p = 0.02$
SAC	3	267	272	-0.43 (-0.56, -0.31)	$p = 0.90$, $I^2 = 0\%$	$p < 0.00001$
GPC	1	109	110	-0.60 (-0.77, -0.43)	Not applicable	$p < 0.00001$
VKC	1	20	20	-1.51 (-1.83, -1.19)	Not applicable	$p < 0.00001$
Double blind	3	238	240	-0.51 (-0.65, -0.37)	$p = 0.32$, $I^2 = 12\%$	$p < 0.00001$
Single blind	2	158	162	-0.98 (-2.00, 0.05)	$p < 0.00001$, $I^2 = 97\%$	$p = 0.06$

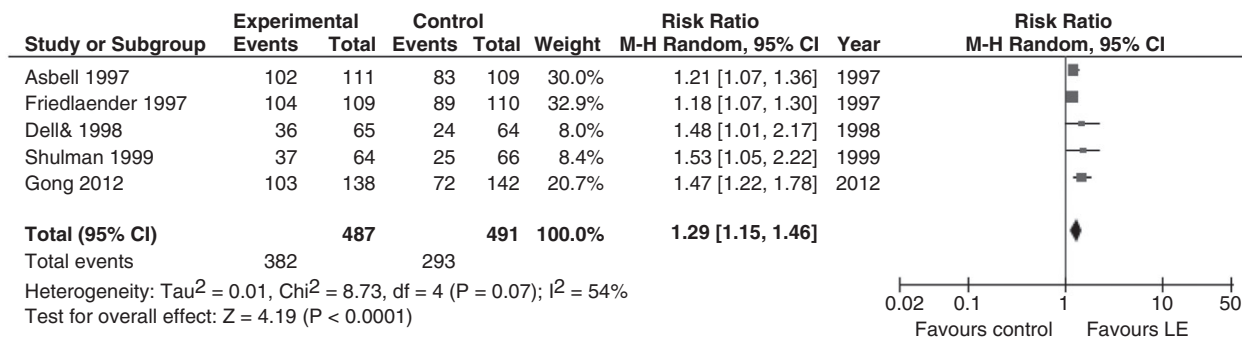


Figure 6. Graph showing the effect of topical LE vs control treatment on the proportion of patients with improvement of allergic symptoms.

Incidence of clinically significant IOP elevation

Six studies were included in this analysis, and a total 15 patients (12 in the LE group and three in the placebo group) had a clinically significant IOP elevation (Table 7). Totally, topical LE showed a higher rate of clinically significant IOP elevation compared to control therapy (placebo and olopatadine), the pooled OR was 3.03 (95% CI = 1.04–8.80; $I^2 = 46\%$; Figure 7).

However, it was noted that some patients with IOP elevation in two studies^{14,20} included were subjects already classified as 'corticosteroid responders' at baseline. Then, we made sensitivity analysis to assess the effect of

corticosteroid response at baseline on the IOP elevation. Topical LE showed a significantly greater IOP-provoking effect than control treatment in the subgroup of 'corticosteroid responder', and a similar effect as control in the sub-group not including 'corticosteroid responder'.

Of those 12 patients taking topical LE who had criterion IOP elevation, 11 were from trials in which wearing of contact lenses was allowed during the study. Topical LE was associated with numerically greater incidence of clinically significant IOP elevation than control treatment in the sub-group of 'wearing of

Table 6. Proportion of patients with improvement of allergic symptoms.

	No. of trials	Crude rate		RR (95% CI)	Test for heterogeneity	Test for overall effect
		LE	Comparison intervention			
All trials	5	382/487	293/491	1.29 (1.15, 1.46)	$p = 0.07$, $I^2 = 54\%$	$p < 0.0001$
No heterogeneous	4	279/349	221/349	1.26 (1.16, 1.38)	$p = 0.27$, $I^2 = 23\%$	$p < 0.0001$
Placebo	4	279/349	221/349	1.26 (1.16, 1.38)	$p = 0.27$, $I^2 = 23\%$	$p < 0.00001$
Positive control	1	103/138	72/142	1.47 (1.22, 1.78)	Not applicable	$p < 0.00001$
0.2%LE	3	176/267	121/272	1.48 (1.27, 1.74)	$p = 0.99$, $I^2 = 0\%$	$p < 0.00001$
0.5%LE	2	206/220	172/219	1.19 (1.10, 1.29)	$p = 0.77$, $I^2 = 0\%$	$p < 0.00001$
SAC	3	176/267	121/272	1.48 (1.27, 1.74)	$p = 0.99$, $I^2 = 0\%$	$p < 0.00001$
GPC	2	206/220	172/219	1.19 (1.10, 1.29)	$p = 0.77$, $I^2 = 0\%$	$p < 0.00001$
Double blind	4	279/349	221/349	1.26 (1.16, 1.38)	$p = 0.27$, $I^2 = 23\%$	$p < 0.0001$
Single blind	1	103/138	72/142	1.47 (1.22, 1.78)	Not applicable	$p < 0.00001$
Allocation concealment	4	346/422	269/427	1.28 (1.13, 1.45)	$p = 0.06$, $I^2 = 59\%$	$p = 0.0001$
Unclear allocation concealment	1	36/65	24/64	1.48 (1.01, 2.17)	Not applicable	$p = 0.05$

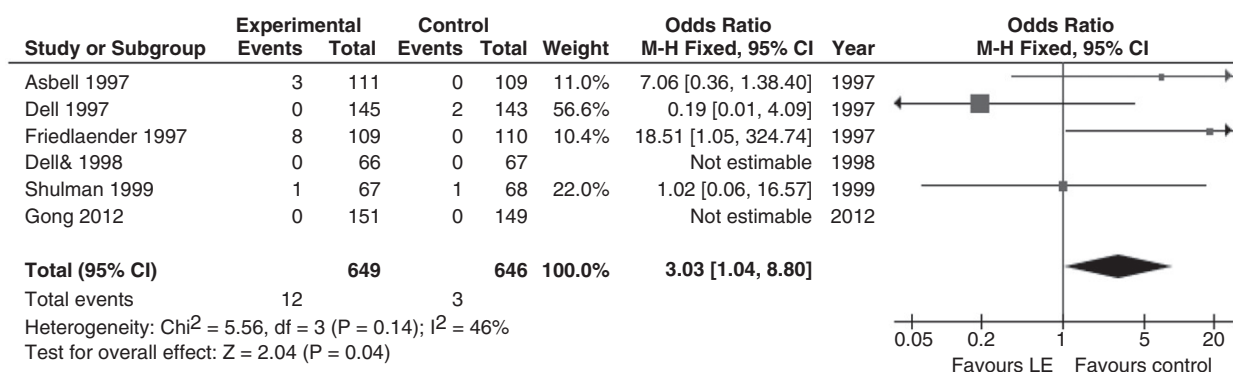


Figure 7. Graph showing the effect of topical LE vs control treatment on the proportion of patients with clinically significant IOP elevation.

Table 7. Proportion of patients with clinically significant IOP elevation.

	No. of trials	Crude rate of clinically significant IOP elevation		OR (95% CI)	Heterogeneity	Overall effect
		LE	Comparison intervention			
All trials	6	12/649	3/646	3.03 (1.04, 8.80)	$p = 0.14$, $I^2 = 46\%$	$p = 0.04$
Corticosteroid responder	2	11/220	0/219	12.61 (1.63, 97.28)	$p = 0.64$, $I^2 = 0\%$	$p = 0.02$
No corticosteroid responder	4	1/429	3/427	0.42 (0.06, 2.90)	$p = 0.43$, $I^2 = 0\%$	$p = 0.38$
Placebo	5	12/498	3/497	3.03 (1.04, 8.80)	$p = 0.14$, $I^2 = 46\%$	$p = 0.04$
Positive control	1	0/151	0/149	Not estimable	Not applicable	Not applicable
0.2% LE	3	1/284	1/284	1.01 (0.06, 15.90)	Not applicable	$p = 0.99$
0.5% LE	3	11/365	2/362	3.05 (0.21, 45.22)	$p = 0.08$, $I^2 = 60\%$	$p = 0.42$
Wearing contact lenses	2	11/220	0/219	12.61 (1.63, 97.28)	$p = 0.64$, $I^2 = 0\%$	$p = 0.02$
No contact lenses	4	1/429	3/427	0.42 (0.06, 2.90)	$p = 0.43$, $I^2 = 0\%$	$p = 0.38$
Double blind	5	12/498	3/497	3.03 (1.04, 8.80)	$p = 0.14$, $I^2 = 46\%$	$p = 0.04$
Single blind	1	0/151	0/149	Not estimable	Not applicable	Not applicable
Allocation concealment	5	12/583	3/579	3.03 (1.04, 8.80)	$p = 0.14$, $I^2 = 46\%$	$p = 0.04$
Unclear allocation concealment	1	0/66	0/67	Not estimable	Not applicable	Not applicable

contact lenses', and the result in the sub-group of 'no wearing of contact lenses' was not statistically significant. Both two concentrations of topical LE showed no statistically significant difference in rate of IOP elevation, compared with control treatment.

The sensitivity analysis of methodologic quality showed that the effect of IOP elevation was statistically significantly different, comparing topical LE with control treatment, which suggested that the study design was not a significant factor.

Discussion

Allergic conjunctivitis is a group of ocular surface diseases that are typically associated with type 1 hypersensitive reactions²¹. Numerous classes of pharmaceutical preparations are available to manage allergic conjunctivitis including ophthalmic antihistamines, mast cell stabilizers, a combination of both antihistamines and mast cell stabilizers (i.e., olopatadine), non-steroidal anti-inflammatory drugs, and topical ophthalmic steroids (i.e., fluorometholone acetate and LE)⁶. Those agents differ in their mechanisms of action, and vary in the efficacy and safety. Antihistamine mast-cell stabilizer (i.e., olopatadine) could block histamine, stabilize the mast cell, and inhibit the activation and migration of eosinophil²². Corticosteroids, of particular interest, could inhibit, block, or reduce the production of all inflammatory mediators in the inflammatory cascade²². Topical antihistamine mast-cell stabilizers and corticosteroids are the mainstay of management for allergic conjunctivitis.

Our meta-analysis of the efficacy and safety of topical LE vs control treatment including placebo, olopatadine, and fluorometholone acetate for treating allergic conjunctivitis enrolled eight RCTs according to the inclusion criteria. Because topical prednisolone acetate is not the first choice for allergic conjunctivitis due to adverse reactions, we extracted the data about topical LE and fluorometholone acetate in the trial of Öner *et al.*¹³ for analysis. Our results showed that topical LE was significantly superior to placebo and not inferior to positive control treatment (olopatadine and fluorometholone acetate) in relieving the signs and symptoms of SAC, GPC, and VKC. Similar results were reported by Cheng *et al.*²³ that topical LE showed significant benefits for SAC and GPC compared with placebo in all five trials, and the pooled risk differences of inflammation improvement were: 28% (95% CI = 19–37%) for SAC, and 26% (95% CI = 18–35%) for GPC, respectively.

Adverse effects analysis revealed that the incidence of clinically significant IOP elevation in LE group was higher than that of the control group, but it was influenced by the response to corticosteroids of the individual patient^{24,25}. The potential of LE to elevate IOP in subjects known to respond to corticosteroids has been reported previously, but the propensity was much less than traditional corticosteroids prednisolone acetate: the proportion of patients with clinically significant IOP elevation in the LE group was 10% (1/10), which was less than that of the prednisolone acetate group (5/9, 55%)²⁴. Besides, we also found IOP increasing effect of LE was influenced by the factor of wearing contact lenses. Because the factor of wearing contact lenses co-exists with the 'corticosteroids responder' in the same two trials^{14,20}, we could not make a conclusion about which factor or both of them take responsibility for the results. Novack *et al.*²⁵ speculated that contact lenses

may act as a reservoir and then increased the possibility of LE-induced IOP elevation. Further, our analysis showed that the incidence of IOP elevation in the 0.5% LE group was 3.01% (11/365), numerically greater than that in the 0.2% LE group (0.35%, 1/284), the placebo group (0.60%, 3/497) and the olopatadine group (0/149). Beyond our expectation, the meta-analysis demonstrated that the difference was not statistically significant. A previous analysis about the effect of long-term use of topical LE on IOP reported similar results: the incidence of IOP elevation with 0.5% LE was 2.1% (14/664), higher than that of vehicle 0.46% (2/432), and the incidence of IOP elevation with 0.2% LE was 0.8% (1/133), similar to that of vehicle 0.7% (1/135)²⁵. The possible explanation for this phenomenon is that the rapid deactivation of topical LE reduces the concentration of the active drug in the aqueous fluid and trabecular meshwork, and then lowers the propensity of the IOP elevation²⁴. Whether the concentration of topical LE relates to that of the active drug in the aqueous humor, and then the incidence of IOP elevation was undetermined. In general, our analysis showed that topical LE-induced IOP elevation was affected by the response to corticosteroid of the individual patient, the wearing of contact lenses, and maybe the concentration of topical LE^{24,25}.

Conclusions

Implications for practice

In summary, the results of our meta-analysis suggested a benefit from topical LE treatment in patients with allergic conjunctivitis. It is more effective than placebo and non-inferior to olopatadine and fluorometholone acetate in alleviating allergic signs and symptoms. However, the IOP elevation associated with topical LE was more frequent than the control treatment. This result should be appreciated with caution because of the clinical heterogeneities across the studies. Patients who are known corticosteroids responders treated with topical LE should be paid special attention to IOP. When instilling topical LE, patients need to be instructed to remove the contact lenses. Further, topical LE 0.2% may possess a better safety profile than LE 0.5% with respect to IOP elevation.

Limitations

There are still some drawbacks of this meta-analysis. First, our study was limited to literatures from the indexed journals and trial registers, some relevant published papers and unpublished data were missed, which may lead to result bias. Second, the number of trials qualified for inclusion was small, so the results have to be interpreted with caution. Third, the included trials vary in term of population,

types of allergic conjunctivitis, concentration of topical LE, follow-up period, and methodologic qualities. Therefore, further large-scale RCTs with larger sample sizes providing sufficient statistical power are still needed to assess the efficacy and safety of different concentrations of topical LE in the treatment of allergic conjunctivitis.

Transparency

Declaration of funding

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Declaration of financial/other relationships

L.-Q. W., X. C., H. L., J.-W. C., and R.-L. W. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. CMRO Peer reviewers on this manuscript have no relevant financial relationships to disclose.

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