

Sublingual immunotherapy for pediatric allergic conjunctivitis: a meta-analysis of randomized controlled trials

Jie Yang, MD¹, Li Zhang, MD², Zhixiang Zhao, MD³ and Shiyu Liao, MD³

Background: Allergic conjunctivitis (AC) is a common chronic condition, especially in children. Ocular symptoms are often overlooked during treatment of allergic rhinoconjunctivitis (ARC). Pediatric ARC can be effectively treated using sublingual immunotherapy (SLIT), which is a guideline-recommended safe treatment approach. However, the therapeutic efficacy of SLIT in terms of ameliorating eye symptoms has not been effectively evaluated.

Methods: We performed a meta-analysis of randomized controlled trials (RCTs) evaluating the use of SLIT for infants, children, and adolescents (aged from 3 to 18 years) with AC or ARC. We searched the Cochrane Library database, EMBASE, and Medline from November 1990 to 2017 to find papers dealing with the effects of SLIT on pediatric AC or ARC. We used standardized mean differences (SMDs) to assess therapeutic effects, employing a random effects model. Subgroup and sensitivity analyses were also conducted. The I^2 metric was used to evaluate heterogeneity.

Results: In total, 13 clinical RCTs were included in our meta-analysis. SLIT reduced ocular symptoms to a level below

that of controls (SMD = -0.21 ; 95% confidence interval [CI], -0.41 to -0.01 ; $p = 0.04$; $I^2 = 55\%$). Notably, on subgroup analysis, SLIT clearly reduced pollen-induced pediatric AC (SMD = -0.36 ; 95% CI, -0.53 to -0.19 ; $p < 0.0001$; $I^2 = 25\%$) but not mite-induced AC (SMD = 0.20 ; 95% CI, -0.20 to 0.60 ; $p = 0.34$; $I^2 = 46\%$).

Conclusion: SLIT relieved ocular symptoms in children with ARC or AC. To confirm these results, future meta-analyses should evaluate high-quality, large-scale population-based trials. © 2018 ARS-AAOA, LLC.

Key Words:

sublingual immunotherapy; pediatric; allergy; conjunctivitis; meta-analysis

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Allergic conjunctivitis (AC) is induced by mast cell activation and includes different forms of ocular inflammation, affecting the cornea, eyelids, and conjunctiva.¹ Its most common symptoms are swelling, tearing, redness, and itching.^{2,3} The most frequent corneal syndrome is temporary blurred vision.⁴ The population-wide frequency of ocular hypersensitivity is $>20\%$ in the United States

and approximately 18% in the United Kingdom.² AC is strongly associated with allergic rhinitis (AR); almost 90% of AR patients experience at least 1 day of ocular problems weekly.^{5,6} Allergic disease is the most frequent chronic condition of children, and ocular hypersensitivity is 1 of the most common ocular disorders encountered in clinical practice. Different studies have provided varying prevalence of allergic diseases in children (aged 6 to 14 years), from 0.3% to 20.5%, which is gradually increasing.⁷

Today, anti-allergic therapeutic agents (mast cell stabilizers, multiple-action anti-allergic agents, and antihistamines) are the mainstays of ocular hypersensitivity management. However, these therapies provide only short-term relief from symptoms. Specific immunotherapy is a guideline-recommended treatment for allergic rhinoconjunctivitis (ARC).⁸ The World Allergy Organization has considered sublingual immunotherapy (SLIT) to be highly efficacious in the treatment of ARC; this has also been supported by other studies.⁹ Ocular symptoms are often

¹Department of Ophthalmology, Zhejiang Hospital, Hangzhou, Zhejiang, China; ²Department of Ophthalmology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; ³Department of Otorhinolaryngology, Zhejiang Hospital, Hangzhou, Zhejiang, China

Correspondence to: Shiyu Liao, M.D., Department of Otorhinolaryngology, Zhejiang Hospital, Lingyin Road no.12, Hangzhou, Zhejiang, 310013, China; e-mail address: shiyuliao90@hotmail.com

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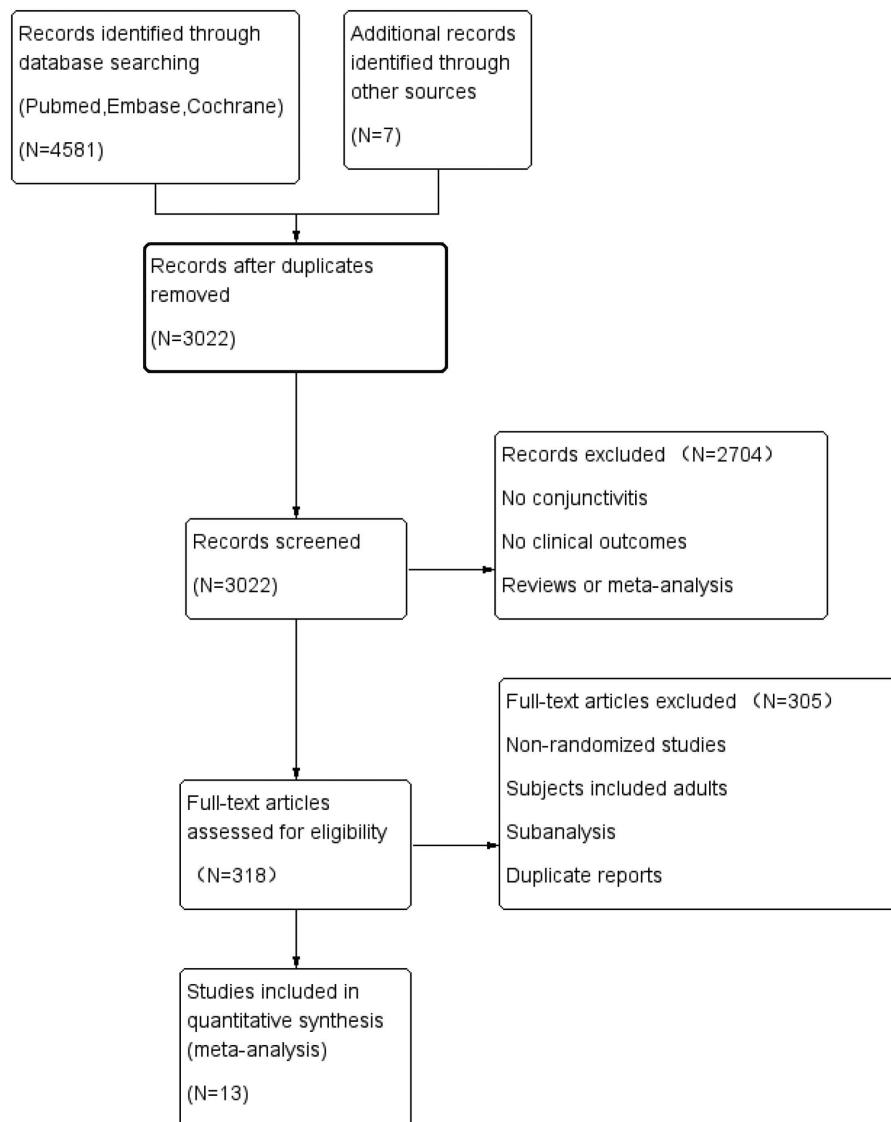


FIGURE 1. Classification of material reviewed for this meta-analysis.

overlooked during the treatment of ARC. A few early trials of SLIT treated pediatric ARC with a focus on conjunctival symptoms. Later, some randomized controlled trials (RCTs) explored the therapeutic effects of SLIT on ocular syndromes in patients with ARC.^{10,11}

A 2011 meta-analysis¹² indicated that SLIT efficiently relieved all or some ocular symptoms in patients (both adult and children) with ARC or AC. However, there is a lack of sufficient evidence on the efficacy of SLIT in the treatment of pediatric ARC or AC patients. We, thus, systematically reviewed and performed a meta-analysis of published RCTs exploring the efficacy of SLIT in pediatric AC patients.

Materials and methods

We retrieved high-quality RCTs exploring the utility of SLIT in the treatment of AC and ARC pediatric patients in

the period of 1990 to 2017 from the EMBASE, MEDLINE, and Cochrane Library databases. Only studies reporting ocular syndrome scores were evaluated. We used the following terms (“allergic” or “hypersensitivity” or “hay fever” or “rhinoconjunctivitis” or “conjunctivitis” or “rhinitis” or “eye diseases”) and (“desensitization” or “immunotherapy” or “immunologic”) and (“sublingual” or “swallow”) to perform article search. Some reports followed up the same patients at different intervals; those research works featuring only the longest intervals were evaluated to prevent duplication. When various results from the same RCTs appeared in multiple reports, we included all studies that lacked overlapping information. We requested additional data from authors and study sponsors when the published information could not be subjected to meta-analysis. For RCTs with multiple interventions and control arms, the placebo groups were deemed controls and the SLIT groups that received

TABLE 1. Characteristics of the included studies

Study (year)	Country	Age (years) mean (range) ^a	Allergen	Modality	Cumulative dose	Follow-up (months)	N (all)	Not located ^b	Outcomes assessed
Tari et al. ¹³ (1990)	Italy	(5–12)	Mites	Drops	363 STU	18	66	8	ESS
Hirsch et al. ¹⁴ (1997)	Germany	10.6 (6–16)	Mites	Drops	570 µg	12	30	12	ESS
Vourdas et al. ¹⁵ (1998)	Greece	12 (7–17)	Olive	Drops	30000 IR	5	66	2	EDSS
La Rosa et al. ¹⁶ (1999)	Italy	10(6–14)	Parietaria	Drops	75000 IR	24	41	8	EDSS
Caffarelli et al. ¹⁷ (2000)	Italy	8.4 (4–14)	Grass mix	Tablets	37250 AU	3	278	12	OSS
Rolinck-Werninghaus et al. ¹⁸ (2004)	Germany	(3–14)	Grass mix	Drops	188 µg	32	97	20	ESS
Valovirta et al. ¹⁹ (2006)	Finland	(5–15)	Grass mix	Drops	200000 SQ-U; 24000 SQ-U	3	98	14	EDSS
Wahn et al. ²² (2009)	Multi-center	10.9 (5–17)	Grass mix	Tablets	NA	4	278	12	ESS
Bufe et al. ²⁰ (2009)	Germany	10.2 (5–16)	Grass mix	Tablets	75000 SQ-T	6	253	19	ESS
Stelmach et al. ²¹ (2009)	Poland	8.9 (6–17)	Grass mix	Drops	43800 IR	24	50	15	OSS
Stelmach et al. ²⁴ (2012)	Poland	8.9 (6–18)	Grass mix	Drops	7300 µg; 3600 µg	24	60	6	OSS
de Bot et al. ²³ (2012)	Netherlands	11.7 (6–18)	Mites	Drops	435 µg	24	257	31	ESS
Aydogan et al. ²⁵ (2013)	Turkey	(5–10)	Mites	Drops	44500 IR	12	18	2	TCSS

^aMean and/or range as provided in the study cited.

^bThe number of lost to follow-up.

AU = allergic units; EDSS = eyes daily symptom score; ESS = eyes symptom score; IR = index of reactivity; N = sample size; NA = not available; OSS = ocular symptom score; SQ-T = standardized quality tablet; SQ-U = standardized quality units; STU = specific treatment units; TCSS = total conjunctivitis symptom scores.

treatments similar to the U.S. Food and Drug Administration (FDA)-approved dose plan were the test groups. The reports featured several ocular symptom scoring systems for AC patients and a single ocular symptom scoring system for ARC patients. We prioritized conjunctivitis symptom scores. Thus, we analyzed all studies to determine the effectiveness of SLIT in the treatment of pediatric AC patients.

Data extraction

We extracted demographic data and the unique characteristics of all studies, including definitions, conjunctivitis-related outcomes, population features, study durations, doses and dose modalities, indications for therapy, sample sizes, journal titles, years of publication, and investigators. The mean differences (means) with standard deviations (SDs) were used to compare continuous outcomes. Two investigators (J.Y. and S.L.) independently extracted all data; any difference was resolved by consensus.

Quality assessment

We used the Cochrane Collaboration Risk of Bias tool of Review Manager 5.3 (RevMan 5.3; The Cochrane Collaboration, London, UK; <http://community.cochrane.org/help/tools-and-software/revman-5>) to evaluate the risk of bias in all RCTs.

Statistical analysis

We evaluated the ocular symptom scores and used the standardized mean differences (SMDs) to assess the treatment effects by employing a random effects model. Heterogeneity was evaluated with the aid of the I^2 metric; an I^2 value >75% indicated significant heterogeneity. Subgroup and sensitivity analyses were conducted to explore the sources of heterogeneity and remove outliers. We employed RevMan 5.3 to perform direct pairwise comparisons of each treatment modality compared with placebo. Primary therapeutic effects were defined as decreases in the ocular symptom scores of pediatric AC or ARC patients. We explored publication bias by constructing funnel plots and via Egger regression, which indicates whether effect sizes are present.

Results

Study selection

Of the 4588 citations initially retrieved, we finally evaluated 13 eligible clinical RCTs^{13–25} that evaluated 1592 pediatric AC or ARC patients randomized to different treatment groups. We excluded all non-RCTs, papers with inadequate data, and duplicate reports (Fig. 1).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aydogan 2013	+	+	+	+	+	+	?
Bufe 2009	?	?	+	+	+	+	+
Caffarelli 2000	+	+	+	+	+	+	+
de Bot 2012	+	+	+	+	+	+	+
Hirsch 1997	+	+	+	+	+	+	+
LaRosa 1999	?	+	+	+	+	+	+
Rolinck - Werninghaus 2004	?	?	+	+	?	+	+
Stelmach 2009	+	+	+	+	?	+	?
Stelmach 2012	+	+	+	+	+	+	+
Trai 1990	?	?	+	+	+	+	+
Valovirta 2006	?	+	+	+	+	+	+
Vourdas 1998	?	?	+	+	+	+	+
wahn 2009	+	+	+	+	+	+	?

FIGURE 2. Risk of bias summary.

Population and study characteristics

Table 1 lists the characteristics of all included RCTs. The included children and adolescents were in the age range of 3 to 18 years. The various SLITs used were standardized; 10 studies presented allergens in liquid drops, and the other 3 studies employed tablets.^{17,20,22} The follow-up period ranged from 3 to 32 months. The pediatric patients of 4 RCTs were susceptible to house dust mites. Of all the patients, 161 (10.1%) discontinued SLIT treatment. The cumulative doses varied and were measured in different ways. The risks of bias are shown in Fig. 2.

Outcomes and analysis

Symptom scores

All 13 RCTs allowed quantitative assessment of AC symptom scores, which were significantly reduced by SLIT (SMD = -0.21 ; 95% CI, -0.41 to -0.01 ; $p = 0.04$; $I^2 = 55\%$; (Fig. 3). The funnel plots were symmetrical (Fig. 4).

Subgroup and sensitivity analyses

RCTs employing diverse SLIT modalities were subjected to subgroup analysis (Table 2). Notably, ocular symptom scores decreased only when SLIT featured tablets (not drops; (Fig. 5). Furthermore, SLIT significantly reduced pollen-induced pediatric AC but not mite-induced disease (Fig. 6).

On post hoc sensitivity analysis, a fixed-effects model revealed no significant changes in primary AC outcomes. When trials with small sample numbers (<30) and those with high dropout rates ($>20\%$) were excluded, the AC symptom scores did not change significantly. The sensitivity data are shown in Table 3.

Publication bias

Both visual inspection of funnel plots and Egger regression ($p = 0.9277$) indicated that publication bias was not present. The fact that we included only 13 trials may limit the power of Egger regression data.

Discussion

We performed a meta-analysis of data from 13 RCTs and confirmed that SLIT relieved ocular symptoms among 1592 pediatric AC or ARC patients randomized to different treatment groups. To the best of our knowledge, the first meta-analysis¹² of SLIT treatment for AC was published in 2011. However, the therapeutic effects of SLIT on ocular symptoms in children have not been effectively analyzed. Based on our findings, we can state that SLIT (compared with placebo) significantly relieved individual and overall ocular symptom scores (redness, itchiness, and watery eyes) in pediatric AC or ARC patients. Unfortunately, we have not found an RCT that evaluates pediatric AC directly. All RCTs assessed SLIT treatment of ARC and did not focus on conjunctivitis symptoms. Here, it should be noted that conjunctivitis symptoms were not analyzed in early RCTs evaluating SLIT in pediatric ARC. However, recent RCTs have paid more attention to such symptoms, improvements in which have been separately evaluated.

SLIT effectively treated pollen-induced pediatric AC ($p < 0.0001$) but not mite-induced AC ($p = 0.34$). Interestingly, earlier studies^{26–28} have reported similar results in pediatric AR patients. It was concluded that SLIT effectively treated pediatric AR caused by grass pollen but was less effective against house dust mite-induced pediatric AR. More clinical trials are required to explore the efficacy of SLIT in dust mite-induced pediatric AC or ARC, as also suggested by others.^{29,30} The heterogeneity of the reductions

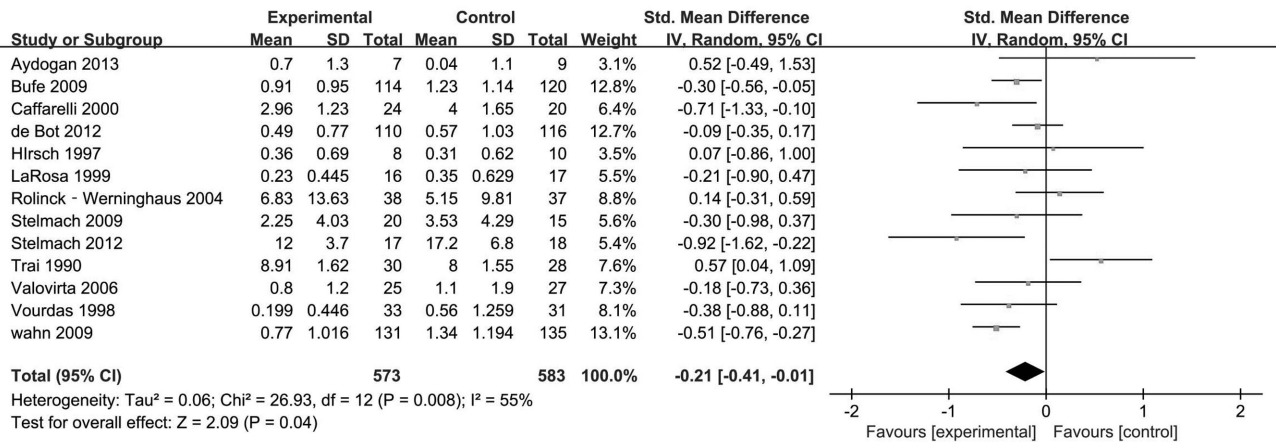


FIGURE 3. Ocular symptom scores.

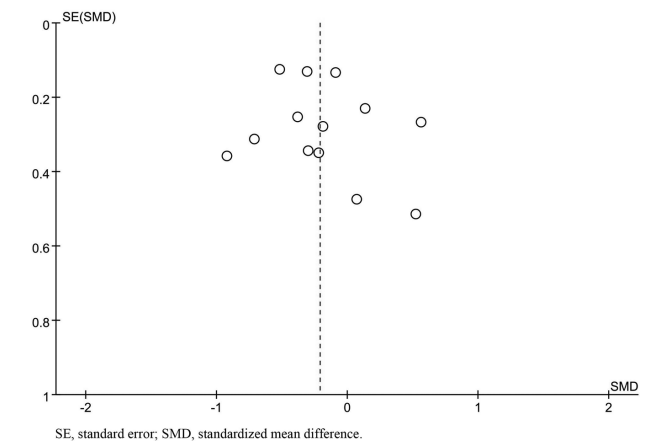


FIGURE 4. Funnel plot for ocular symptom scores. SE = standard error of the mean; SMD = standardized mean difference.

in pollen-induced pediatric AC was low ($I^2 = 25\%$) among 9 relevant studies, suggesting that SLIT was better than the current standard therapy in terms of treating seasonal AC. Subgroup analysis showed that SLIT treatment of pediatric AC or ARC (as evaluated by conjunctivitis symptom

scores) was effective when tablets ($p < 0.00001$), but not drops ($p = 0.47$), were given. All RCTs featuring tablets exhibited significant reductions in ocular symptoms. However, some RCTs using drops exhibited no decrease in symptom scores. The various SLIT modalities featured similar immunologic mechanisms; treatment efficacy depended on patient compliance, cumulative dose, and allergen type. According to our subgroup analysis, the efficacy of SLIT in drop form is less certain, although both SLIT modalities are recommended by guidelines and proven to be efficacious for ARC. Perhaps, this phenomenon is attributable to the short duration of treatment and inappropriate cumulative doses, as suggested by some included studies.^{13,23} The efficacy of SLIT was notable in tablet studies, with minimal heterogeneity in these studies ($I^2 = 8\%$). Unfortunately, only 3 RCTs featured tablets, which may limit the power of our findings. As also suggested by others,³⁰ the efficacy of tablets should be further explored in high-quality RCTs with larger patient numbers. In terms of reducing medication use, only 2 included RCTs^{20,23} presented the use of eye medications individually. They showed the proportion of day with conjunctivitis medication (levocabastine) use, compared with placebo

TABLE 2. Subgroup analysis of efficacy according to treatment characteristics

Subanalysis	Symptom score				I ² (%)
	Number of studies	Number of patients	SMD (95% CI)	P	
SLIT modalities					
Drops	10	612	−0.09 (−0.32 to 0.15)	0.47	43
Tablets	3	544	−0.44 (−0.62 to −0.26)	<0.00001	8
Allergen types					
Pollen	9	838	−0.36 (−0.53 to −0.19)	<0.0001	25
Mites	4	318	0.20 (−0.20 to 0.60)	0.34	46

CI = confidence interval; SLIT = sublingual immunotherapy; SMD = standardized mean difference.

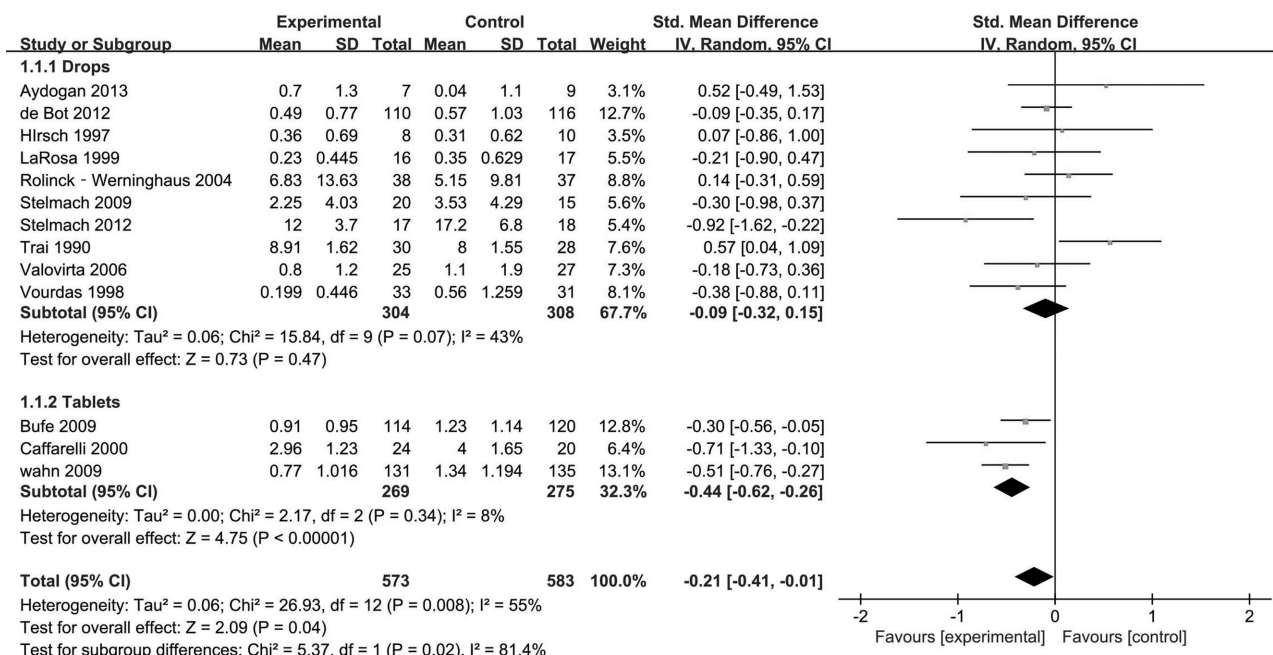


FIGURE 5. Subgroup analysis of efficacy according to different modalities.

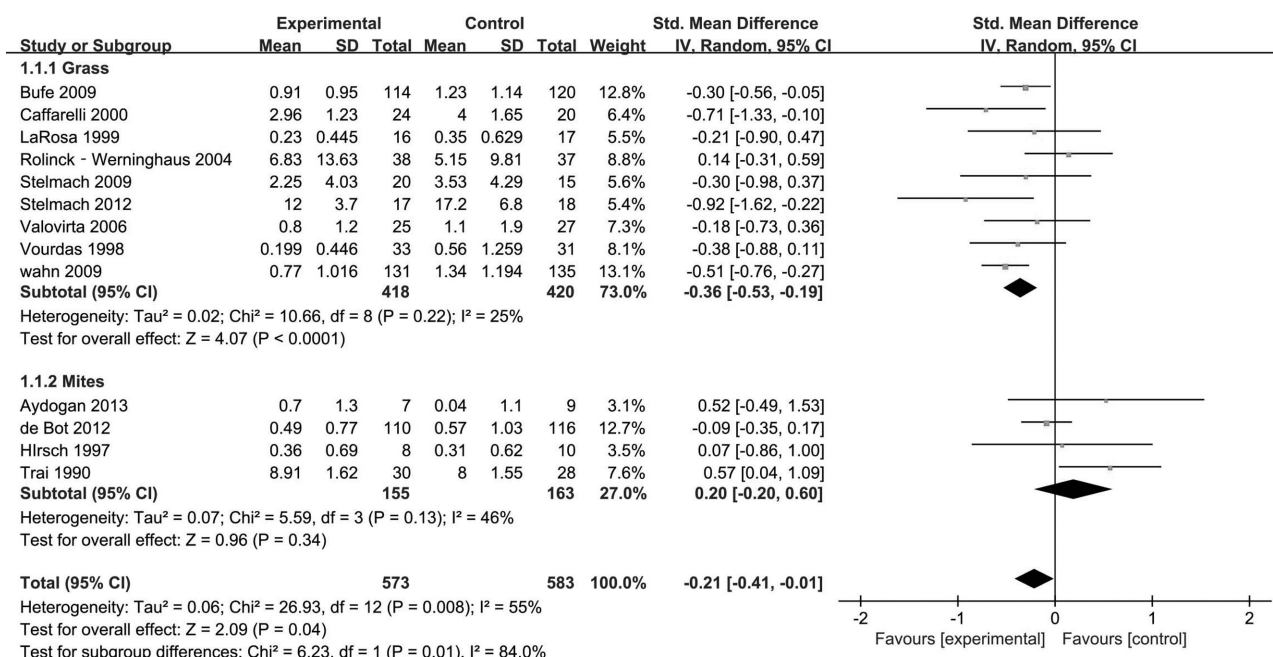


FIGURE 6. Subgroup analysis of efficacy according to different allergens.

TABLE 3. Sensitivity analysis of efficacy

Sensitivity analysis	Symptom score			I^2 (%)
	Number of studies	SMD (95% CI)	p	
Fixed-effects model	13	-0.25 (-0.36 to -0.13)	<0.0001	55
Excluded small studies ($n < 30$)	11	-0.25 (-0.45 to -0.04)	0.02	59
Excluded high dropout rate ($> 20\%$)	10	-0.25 (-0.48 to -0.03)	0.03	62

CI = confidence interval; SMD = standardized mean difference.

groups. The data demonstrated no significant reduction in eye medication use in either group. It is noteworthy that Calderon et al.¹² reported similar results in the first meta-analysis. In short, there is no current evidence suggesting reduced eye medication use in AC or ARC patients.

Our work has certain limitations. Variations in the baseline severity of AC or ARC in pediatric patients, in the ocular scoring systems used, and in the SLIT therapeutic regimens may limit the accuracy of our data. We used a robust measure (SMD) to counter these problems. Also, moderate heterogeneity ($I^2 = 55\%$) was evident. Subgroup analysis revealed that some of this heterogeneity was attributable to the differences in allergens and treatment modalities. Additionally, 46% of all studies had small sample sizes ($n < 30$ in each arm); this was an unavoidable, but

important, methodological limitation. Only 31% of the included RCTs had >100 pediatric patients in each arm. Finally, the methods used to conceal allocation, and therefore, the randomization strategies, were not detailed in some reports. Thus, this reduces the quality of the work as a formal assessment of selection bias was not possible.

Conclusion

This meta-analysis demonstrated that SLIT effectively relieved conjunctivitis symptoms in pediatric AC or ARC patients. This study suggests some benefits for SLIT in the management of inadequately controlled AC or ARC. However, there is a requirement for more high-quality, large-scale population-based RCTs. 🌐

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