

ORIGINAL ARTICLE

Local nasal immunotherapy for allergic rhinitis: A systematic review and meta-analysis

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Abstract

Introduction: Local nasal immunotherapy (LNIT), an alternative noninjection immunotherapy method, is theoretically an efficient method for inducing immunotolerance directly in the affected organ. LNIT is more convenient and less invasive than injection immunotherapy, with fewer systemic reactions. The development of adjuvants to overcome LNIT's limitations raises the possibility of it being an alternative allergen immunotherapy.

Objectives: To evaluate the clinical and immunological efficacy and safety of LNIT for patients with allergic rhinitis.

Methods: A systematic search for randomized controlled trials comparing LNIT and placebo was performed using OVID Medline and Embase. Outcomes were total nasal symptom score (TNSS), symptom-medication score (SMS), medication score, immunological assessment, and nasal provocation threshold. Data were pooled for meta-analysis.

Results: A total of 20 studies with 698 participants were included. The LNIT group had greater posttreatment improvement in TNSS, SMS, and medication score than control (TNSS: standardized mean difference [SMD], −1.37 [95% confidence interval [CI], −2.04 to −0.69]; SMS: SMD, −1.55 [95% CI, −2.83 to −0.28]; and medication score: SMD, −1.09 [95% CI, −1.35 to −0.83]). Immunological assessments showed no significant differences in serum-specific IgE (mean difference [MD], 6.35; 95% CI, −4.62 to 17.31), nasal IgE (MD, −0.59; 95% CI, −1.99 to 0.81), or nasal eosinophil cationic protein (MD, 7.63; 95% CI, −18.65 to 33.91). Only serum IgG significantly increased with LNIT (MD, 0.45; 95% CI, 0.20, 0.70). Posttreatment, nasal provocation threshold was higher with LNIT (MD, 27.30; 95% CI, 10.13–44.46). No significant adverse events were reported.

Conclusions: LNIT is a safe alternative allergen immunotherapy route without significant adverse events. It improves clinical symptoms, reduces medication usage, and increases the nasal provocation threshold.

KEYWORDS

allergic rhinitis, allergy vaccine, local nasal immunotherapy, meta-analysis, nasal administration

1 | INTRODUCTION

Allergic rhinitis (AR) is one of the most common health problems worldwide. Its prevalence ranges from 17% to 28.5% in Europe¹ and from 6.9% to 36% in Asia,^{2,3} and is tending to increase every year.⁴ Treatment options include allergen avoidance and environmental control, various pharmacotherapies (such as topical steroids and oral antihistamines), immunotherapy, nasal turbinate surgery, and alternative medicine (such as acupuncture and herbal therapy).⁵

Allergen immunotherapy (AIT) is the only available curative treatment. It involves repeated allergen administration to modulate the immune response and induce allergen-specific immune tolerance. The main mechanisms are immune deviation in favor of the Th1 response and induction of regulatory T cells. Current evidence shows that immunotherapy can reduce allergic symptoms, minimize medication usage, and prevent new sensitization.⁶

Various routes and AIT delivery systems are available. The most common route of administration is subcutaneous immunotherapy (SCIT) for the injectable route and sublingual immunotherapy (SLIT) for the noninjectable route. Both techniques have demonstrated comparable clinical improvements, with no significant differences between SLIT and SCIT. The standardized mean difference (SMD) in the total nasal symptom score (TNSS) is -0.33 (95% confidence interval [CI], -0.54 to -0.13) for SLIT⁷ and -2.17 (95% CI, -3.50 to -0.84) for SCIT,⁸ relative to placebo. Other AIT routes have been studied. They include epicutaneous immunotherapy, intradermal immunotherapy, oral immunotherapy, bronchial immunotherapy, intralymphatic immunotherapy, and local nasal immunotherapy (LNIT).^{9,10}

LNIT involves the induction of immunotolerance in the nasal cavity. The *in vivo* kinetics of LNIT were first investigated by Bagnasco et al¹¹ in 1997. Nasal dendritic cells in nasal-associated lymphoid tissue (NALT) play a crucial role in AIT-induced priming and dissemination of the immune response.¹² The network of dendritic cells around the nostrils facilitates the uptake of allergen molecules and initiates the adaptive immune response.¹² This may be caused by the induction of direct immunotolerance in the nasal cavity, the affected organ, compared with other noninjectable routes, such as SLIT. A murine model indicated that LNIT could induce the release of interleukin 10

and the desensitization of allergen challenge.¹³ In a human study, LNIT was shown to successfully improve symptoms and medication scores in patients with AR and provide clinical efficacy similar to SCIT.¹⁴

The most recent randomized controlled trial of LNIT was published in 2009.¹⁵ LNIT became less popular because of dosage control difficulty, unsatisfactory patient compliance because of frequent local side effects, and the need for specific administration techniques to avoid allergen spillage into the lower airways.¹⁶

LNIT has received renewed attention with the recent development of delivery systems and adjuvants, such as liposomes and nanoparticles, to overcome its limitations.¹⁷ LNIT has an easy route of administration and can be performed by patients. It is also less time-consuming, less invasive, and has fewer systemic reactions than injection immunotherapy.¹⁶

This systematic review and meta-analysis aimed to evaluate the clinical and immunological efficacy and safety of LNIT for patients with AR. To our knowledge, this is the first publication to analyze pooled LNIT data.

2 | MATERIALS AND METHODS

This systematic review and meta-analysis were registered in PROSPERO (International prospective register of systematic reviews) on April 29, 2021 (registration number: CRD42021252155).

2.1 | Eligibility criteria

We included all randomized controlled trials published in English that compared the effects of LNIT and a control in humans. Studies in either adult or pediatric patients with AR were eligible for inclusion. The accepted diagnostic criteria for AR included clinical symptoms with skin prick test, serum specific IgE, or nasal provocation. Any allergen (perennial or seasonal), type of preparation (solution or powder), delivery method (spray or manual nasal insufflator), dosage, or duration was included. Studies that assessed the following outcomes were eligible: symptom scores, medication scores, serum immunological assessments, nasal cytokine assessments, adverse events (AEs), and nasal provocation thresholds (NPT). However, secondary research studies (eg, reviews) and animal studies were excluded.

2.2 | Search strategy

A systematic search was performed using OVID Medline, the Embase database, and a manual bibliographic search. The search terms were “intranasal,” “local nasal,” “nasal administration,” “immunotherapy,” “allergy vaccine,” “hyposensitization,” “desensitization,” and “allergic rhinitis” (Table S1). The last search was performed on January 12, 2022. Duplicate records were removed.

2.3 | Study selection and data extraction

The title and abstract screening were independently performed by two reviewers (N.K. and P.T.). Irrelevant reports were removed. Three independent reviewers (P.T., P.N., and N.K.) subsequently reviewed the full-text versions of relevant articles according to the specified eligibility criteria. Final decisions were made on study inclusions, with disagreements resolved by group discussion (P.T., P.N., and N.K.). Data extraction and collection were then performed. The following characteristics of the included studies were extracted: year and country of publication, the number of participants, mean age, sex, allergen, preparation form, dosage titration, duration of treatment, and outcome measurements. The outcome assessments of the indoor allergen were extracted from the primary data as the post-treatment evaluation, and the outcome assessments of the outdoor allergen were extracted as the peak-during-season evaluation. Cointerventions were allowed and evaluated in part of the medication score or details of the other treatment modalities. All AEs were recorded, including either local or systemic AEs, especially the rates of the familiar AEs, including rhinorrhea and sneezing. The corresponding authors of articles with incomplete information were contacted for further data.

2.4 | Risk-of-bias assessment

To assess the risk of bias of the included studies, we employed the approach recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*. Six items were considered: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, and selective reporting.¹⁸

2.5 | Data synthesis

Data were pooled for meta-analysis. The effect size of continuous outcome data was reported as the mean difference (MD) or SMD with standard deviation and 95% CIs. When standard deviations were not available, calculations from

standard errors, CIs, t values, and probability (p) values were performed.¹⁸ If any of the studies evaluated more than one allergen, we registered the data for each allergen separately. Statistical analyses were performed with Review Manager, version 5.4 (The Cochrane Collaboration). Labels were reversed if the outcomes were positive.¹⁹ The random-effect model was applied. The heterogeneity measures were Cochran Q test and the I^2 statistic. An I^2 was interpreted as follows: 0% to 40%: might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity, and 75% to 100%: considerable heterogeneity.¹⁸ Subgroup analyses were conducted to assess the potential effects of the related factors in the major clinical outcome, age groups, allergen type (indoor vs outdoor), and year of publication. Considering the technological advancement in vaccine production, most references were published in 1989 and later.^{17,54–58} Thus, the subgroup analysis of studies before and after 1990 based on potential vaccine technology differences was used. Publication bias was reported by funnel plot. Sensitivity analysis was performed to determine whether the effects were still significant.

3 | RESULTS

3.1 | Study selection

The study retrieval and selection process were illustrated in the flowchart in Figure 1. Total 233 records were identified through the Ovid Medline database, and 249 records were identified through the Embase database search. Three more studies were added through a bibliographic search.^{20–22} In all, 388 records were retrieved after duplications were removed. Their titles and abstracts were screened, and 27 records were sought for full-text retrieval. Three full texts could not be retrieved,^{23–25} leaving 24 full texts to be assessed for eligibility. Two studies had comparison groups not compatible with our interest: one with allergoid use and the other without placebo control.^{26,27} Twenty-two studies were included for qualitative evaluation. Data could not be extracted from one study,²⁸ and another was excluded because it was the continuation of another study.²⁹ Note that two studies were separate reports of the clinical response³⁰ and the immunological response of a single clinical trial.³¹ All studies diagnosed AR by clinical symptoms and either skin prick test or serum-specific IgE. Twelve studies had NPT as a part of the diagnostic investigation. The control group received placebo nasal spray containing lactose powder (nine studies),^{20,21,32–35,40,41,43} normal saline (three studies),^{15,22,37} or other diluents (five studies).^{30,31,38,39,44} Three studies did not report the

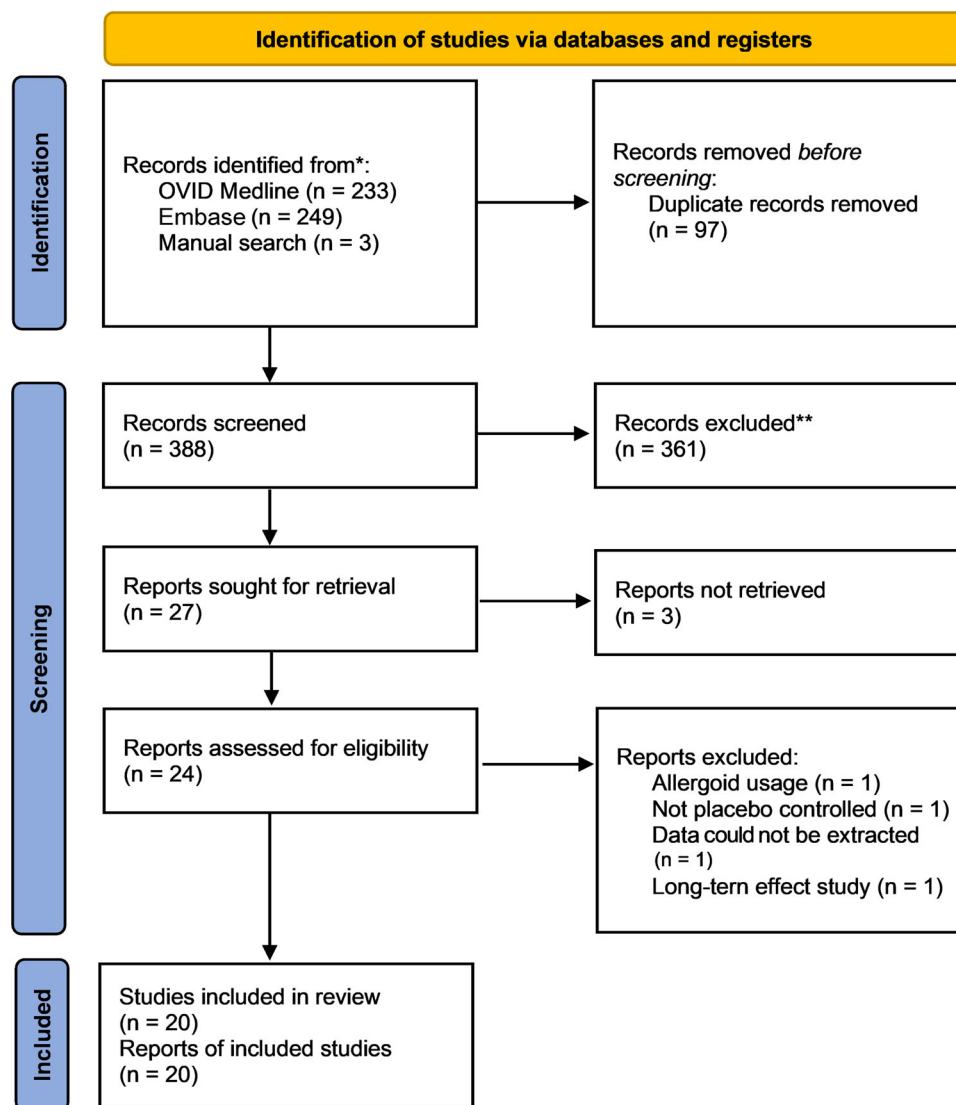


FIGURE 1 Flowchart of study retrieval and selection.

placebo composition.^{14,41,36} There were no cointerventions other than pharmacologic treatment in the included studies. Six studies assessed symptom–medication (SMS) scores^{22,30,35,36,41,43} and 11 studies assessed medication scores as an outcome.^{20–22,30,32,33,36,37,40,41,44}

3.2 | Participants

The 20 included studies had a combined total of 698 participants. The mean age was 30.54 years, ranging from 4 to 67 years. Men predominated slightly (53.1%). AR was diagnosed by clinical symptoms (19 articles), skin prick tests (19 articles), serum-specific IgE (12 articles), or nasal provocation tests (12 articles). The patients were allergic to mites (six trials) and pollen (pellitory, grass, birch, alder, and weed; 15 trials). The immunotherapy applications of outdoor allergens were delivered in a preseasonal period in all articles. The baseline characteristics of the included stud-

ies are detailed in Table 1. The assessments of the risk of bias of the included studies are presented in Figure 2. The sensitivity analysis was performed considering influential data detection (Figure S24–S34). The visualized influential data^{14,15,37} was identified on the following outcomes: TNSS, symptom score, and medication score. The leave-out of these data still demonstrated significant effect of LNIT. Additionally, the I^2 values of all comparison groups decreased to no heterogeneity or moderate heterogeneity. These findings improved the robustness of the study. Funnel plot demonstrated asymmetrical pattern in all outcomes (Figure S12–S23).

3.3 | TNSS: LNIT vs controls

Eleven trials evaluated TNSS as an outcome.^{21,22,30,32–39} The total number of patients for this outcome was 298. The meta-analysis showed that the LNIT group had a greater

TABLE 1 Baseline characteristics of the included studies

Authors	Year	Country	No. of patients (active/placebo)	Mean age (years)	Men (%)	Allergen	Preparation form	Outcome measurements
Amato et al ³³	1995	Italy	26 (13/13)	25.8	42	Pellitory pollen	Powder insufflator	Clinical, medication, immunological, NPT
Andri et al ²⁰	1992	Italy	24 (16/8)	29.7	43.7	Pellitory pollen	Powder insufflator	Clinical, medication, NPT
Andri et al ²¹	1993	Italy	24 (12/12)	19.4	62.5	Mixed mite	Powder insufflator	Clinical, medication, NPT
Andri et al ⁴⁴	1995	Italy	30 (15/15)	36	53.3	Birch pollen	Powder insufflator	Clinical, medication, immunological, NPT
Andri et al ³²	1996	Italy	32 (16/16)	31.4	46.8	Mixed grass pollen	Powder insufflator	Clinical, medication, immunological, NPT
Bertoni et al ²²	1999	Italy	20 (10/10)	29.1	65	Grass pollen	Solution spray	Clinical, medication, NPT
Cirila et al ⁴⁰	1996	Italy	22 (11/11)	33.5	45	Birch-alder pollen	Powder insufflator	Clinical, medication, NPT
Fanales et al ³⁴	1995	Italy	20 (10/10)	25.7	55	Mite <i>DerP</i>	Solution nebulization	Clinical, immunological, NPT
Gaglani et al ³⁵	1997	United States	29 (14/15)	42.9	55.6	Mixed weed pollen	Solution spray	Clinical, immunological, NPT
Georgitis et al ³⁶	1983	United States	50 (34/16)	36.2	61.3	Mixed grass	Solution spray	Clinical, medication, immunological
Georgitis et al ⁴¹	1984	United States	45 (29/16)	34.2	55.6	Mixed grass	Solution spray	Clinical, medication, immunological
Giannarini et al ¹⁴	1998	Italy	45 (30/15)	NR	NR	Mixed grass	Powder insufflator	Clinical, immunological
Marcucci et al ³⁷	2002	Italy	32 (16/16)	9.2	53.1	Mixed mite	Powder insufflator	Medication, immunological, NPT
Motta et al ⁴²	2000	Italy	102 (54/48)	26	52.7	Mixed mite, mixed pellitory, and grass pollen	Powder insufflator	Clinical
Nickelsen et al ³⁰	1981	United States	75 (53/22)	36	48.8	Ragweed pollen	Solution spray	Clinical, medication, NPT
Nickelsen et al ³¹	1981	United States	75 (53/22)	36	48.8	Ragweed pollen	Solution spray	Immunological
Passalacqua et al ⁴³	1997	Italy	20 (10/10)	33	55	Pellitory pollen	Powder insufflator	Clinical
Passali et al ³⁸	2002	Italy	36 (18/18)	24.3	55.6	Mixed mite	Powder insufflator	Clinical, NPT
Tsai et al ¹⁵	2009	Taiwan	35 (24/11)	29.7	54.2	Mite <i>DerP</i>	<i>DerP</i> -coated strip	Clinical, immunological
Welsh et al ³⁹	1981	United States	33 (18/15)	31	51.5	Short ragweed	Solution spray	Clinical, medication, immunological

DerP, *Dermatophagoides pteronyssinus*; NB, nebulization; NPT, nasal provocation threshold; NR, not reported.

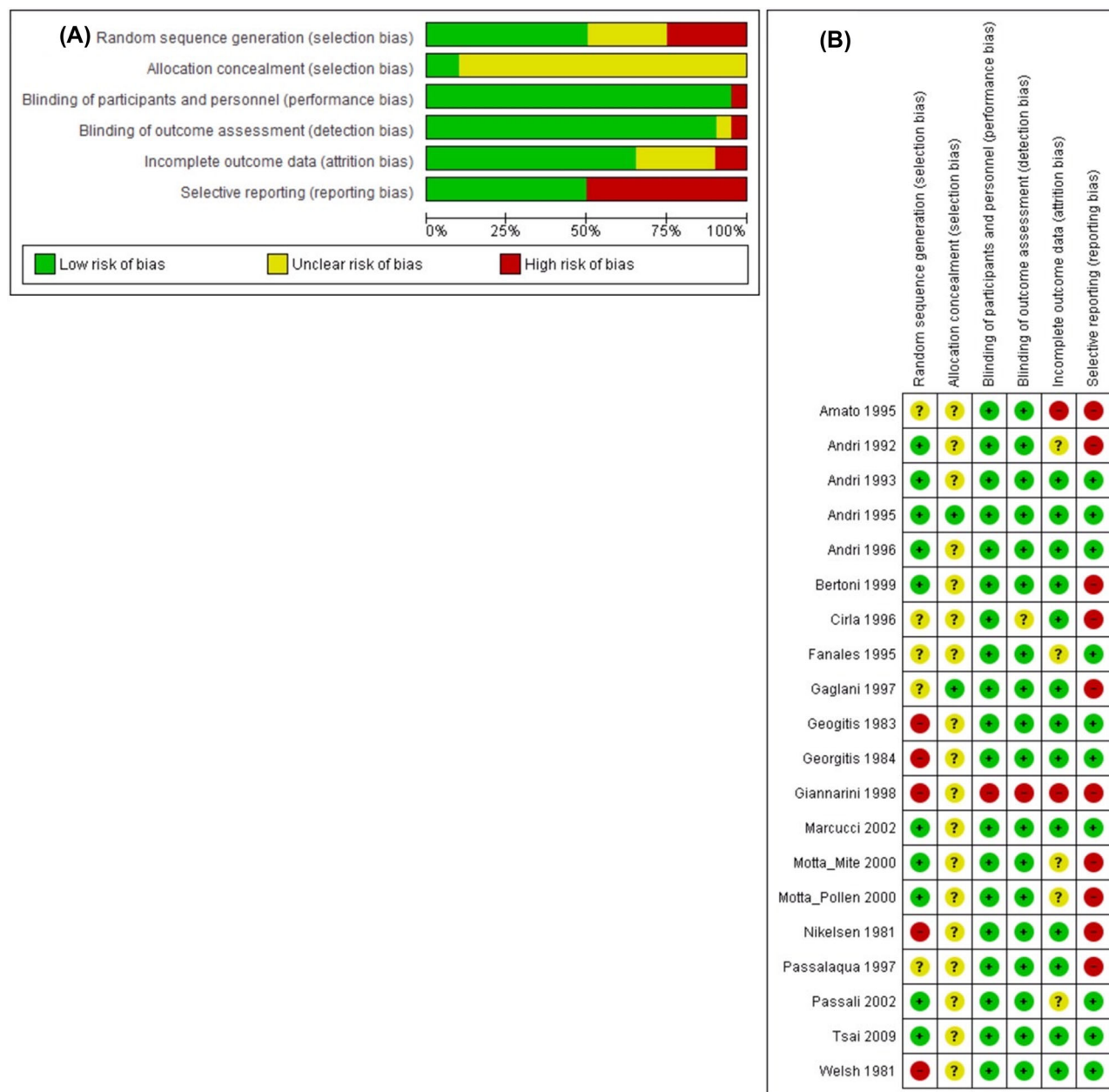


FIGURE 2 The risk of bias assessment. (A) Risk-of-bias graph, (B) risk-of-bias summary.

posttreatment improvement than the control group (SMD, -1.37 ; 95% CI, -2.04 to -0.69 [$p < 0.0001$]). There was substantial heterogeneity ($I^2 = 84\%$) (Figure S1).

3.3.1 | TNSS subgroup analysis: TNSS by age group

A subgroup analysis was performed by age group (<15 years vs ≥ 15 years). The LNIT group had greater post-treatment improvement than the control group for both age subgroups. The younger age subgroup (SMD, -3.11 ; 95% CI, -4.30 to -1.91) had significant improvement ($p = 0.005$) compared with the older age subgroup (SMD,

-1.17 ; 95% CI, -1.82 to -0.51). The forest plot is shown in Figure 3A.

3.3.2 | TNSS subgroup analysis: TNSS by allergen subtype

A subgroup analysis was conducted by allergen subtype (indoor vs outdoor). The LNIT group had greater post-treatment improvement than the control group for both allergen subgroups. There was no significant difference ($p = 0.99$) between the indoor allergen subgroup (SMD, -1.39 ; 95% CI, -2.53 to -0.25) and the outdoor allergen subgroup (SMD, -1.40 ; 95% CI, -2.32 to -0.48) (Figure S2).

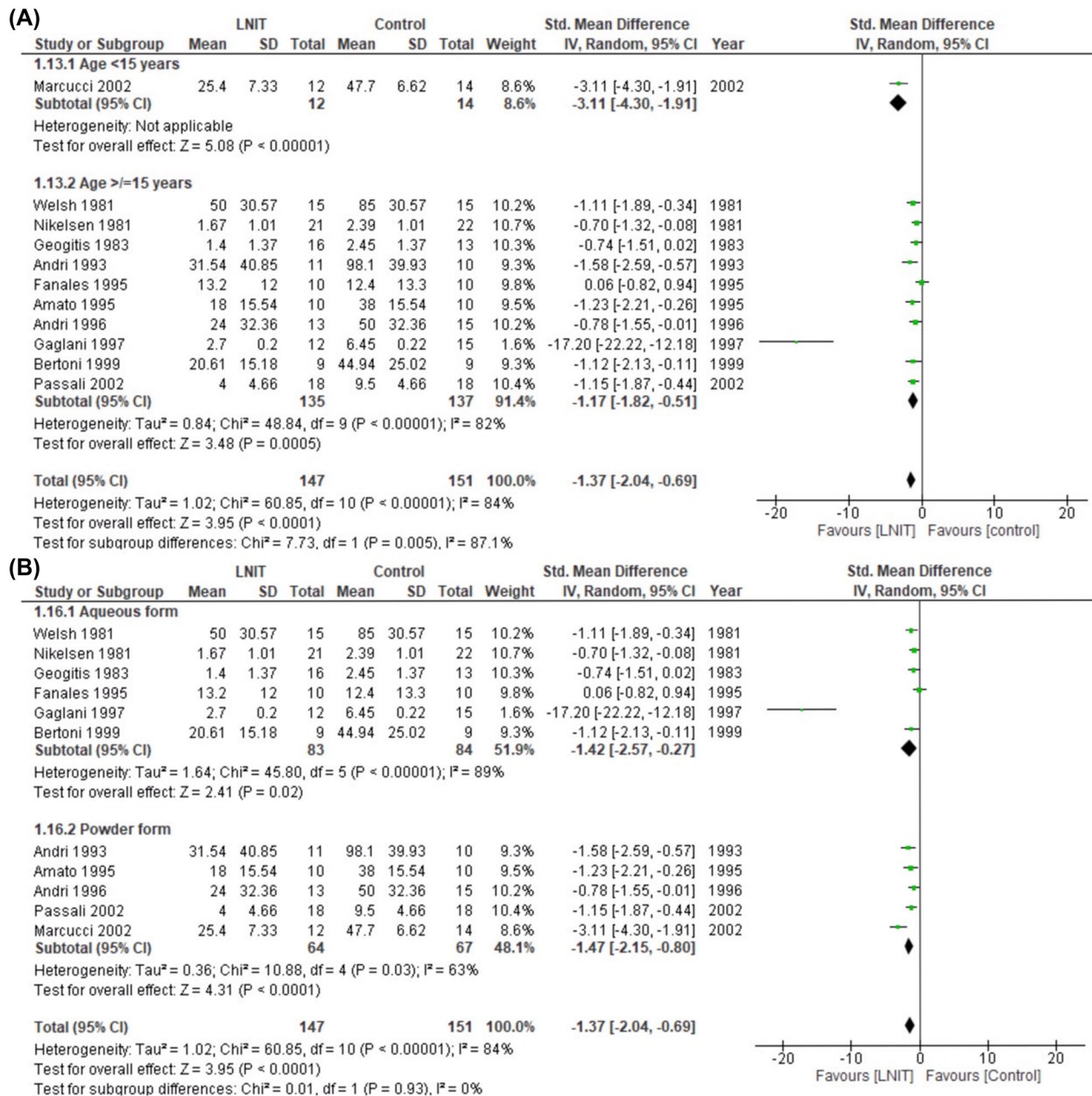


FIGURE 3 Total nasal symptom score: local-nasal immunotherapy vs controls. (A) Subgroup analysis by age group, (B) subgroup analysis by preparation form of local nasal immunotherapy (LNIT). CI, confidence interval.

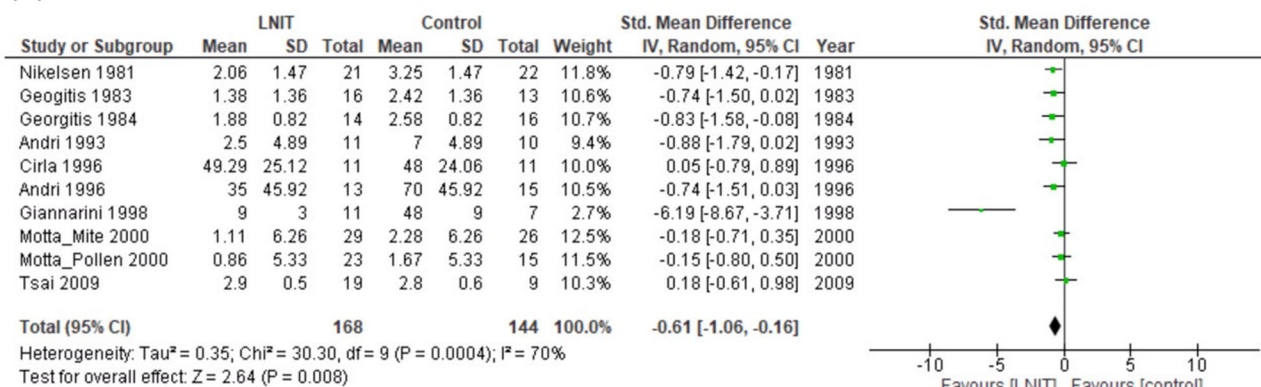
3.3.3 | TNSS subgroup analysis: TNSS by year of publication

A subgroup analysis was performed by year of publication (before 1990 vs after 1990). The LNIT group had a greater posttreatment improvement than the control group for both subgroups. There was no significant difference ($p = 0.09$) between the pre-1990 subgroup (SMD, -0.83 ; 95% CI, -1.24 to -0.42) and the post-1990 subgroup (SMD, -1.79 ; 95% CI, -2.83 to -0.72). (Figure S3)

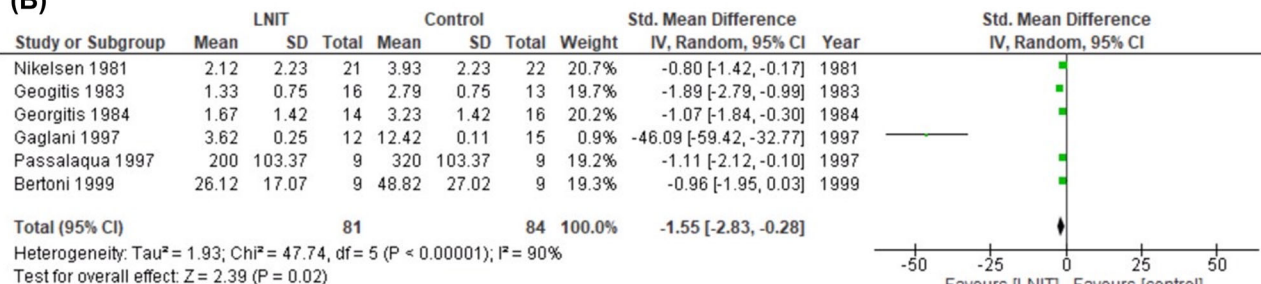
3.3.4 | TNSS subgroup analysis: TNSS by preparation form of LNIT

A subgroup analysis was performed by the preparation form of LNIT (aqueous vs powder). The LNIT group had greater posttreatment improvement than the control group for both subgroups. There was no significant difference ($p = 0.93$) between the aqueous-form subgroup (SMD, -1.42 ; 95% CI, -2.57 to -0.27) and the powder-form subgroup (SMD, -1.47 ; 95% CI, -2.15 to -0.80). The forest plot is illustrated in Figure 3B.

(A)



(B)



(C)

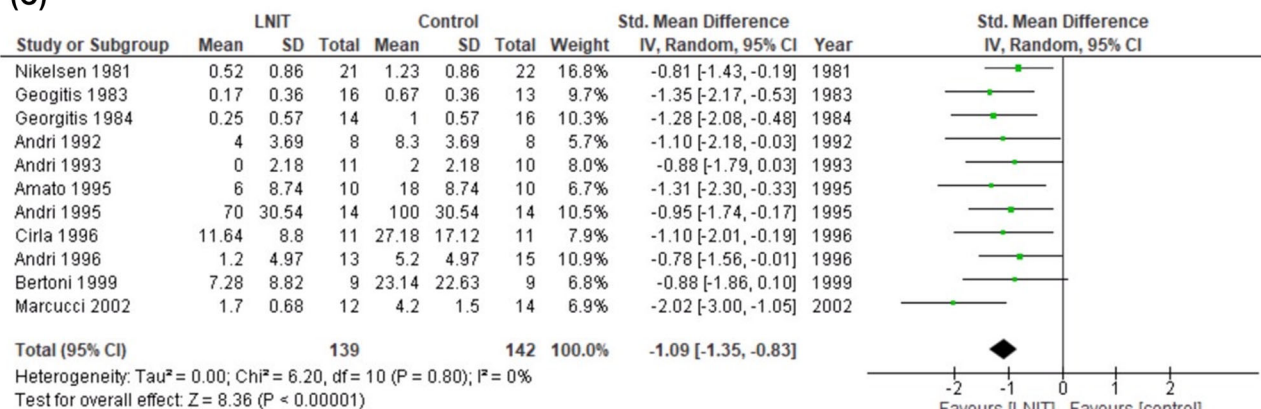


FIGURE 4 Clinical outcomes assessment: local nasal immunotherapy (LNIT) vs controls. (A) Nasal obstruction symptom scores, (B) symptom-medication scores, (C) medication scores.

3.4 | Nasal obstruction: LNIT vs controls

Nine trials assessed nasal obstruction symptom scores as an outcome.^{14,15,21,30,32,36,40–42} The total number of patients for this outcome was 312. The meta-analysis showed that the LNIT group had greater posttreatment improvement than the control group (SMD, -0.61 ; 95% CI, -1.06 to -0.16 [$p = 0.008$]). There was substantial heterogeneity ($I^2 = 70\%$). The forest plot is shown in Figure 4A.

3.5 | Rhinorrhea: LNIT vs controls

Ten trials assessed rhinorrhea symptom scores as an outcome.^{14,15,21,30,32,36,39–42} In all, 305 patients were considered for this outcome. The meta-analysis found that the LNIT group had greater posttreatment improvement than the control group (SMD, -0.69 ; 95% CI, -1.18 to -0.20 [$p = 0.005$]). There was also substantial heterogeneity ($I^2 = 74\%$) (Figure S4).

3.6 | Sneezing: LNIT vs controls

Ten trials assessed sneezing as an outcome.^{14,15,21,30,32,36,39–42} A total of 300 patients were evaluated for this outcome. The meta-analysis revealed that the LNIT group had greater posttreatment improvement than the control group (SMD, -0.72 ; 95% CI, -1.24 to -0.21 [$p = 0.006$]). Substantial heterogeneity was evident ($I^2 = 76\%$) (Figure S5).

3.7 | Itching: LNIT vs controls

Four trials assessed itching symptom scores as an outcome.^{14,32,39,40} Ninety-eight patients were assessed for this outcome. The meta-analysis showed that the LNIT group had greater posttreatment improvement than the control group (SMD, -1.24 ; 95% CI, -2.08 to -0.40 [$p = 0.004$]). Substantial heterogeneity was found ($I^2 = 69\%$) (Figure S6).

3.8 | LNIT vs controls

Six trials assessed SMS as an outcome.^{22,30,35,36,41,43} A total of 165 patients were examined. The meta-analysis found that the LNIT group had greater posttreatment improvement than the control group (SMD, -1.55 ; 95% CI, -2.83 to -0.28 [$p = 0.02$]). The heterogeneity was considerable ($I^2 = 90\%$). The forest plot is presented in Figure 4B.

3.9 | Medication scores: LNIT vs controls

Eleven trials assessed medication scores as an outcome.^{20–22,30,32,33,36,37,40,41,44} In all, there were 281 patients. The meta-analysis identified that the LNIT group had a lower posttreatment medication score than the control group (SMD, -1.09 ; 95% CI, -1.35 to -0.83 [$p < 0.00001$]). Heterogeneity was absent ($I^2 = 0\%$). The forest plot is given in Figure 4B.

3.10 | Serum-specific IgE levels: LNIT vs controls

Four trials assessed serum-specific IgE levels as an outcome.^{14,15,34,37} Ninety-nine patients were evaluated. The meta-analysis did not find significant differences between the LNIT and control groups (MD, 6.35 ; 95% CI, -4.62 to 17.31 [$p = 0.26$]). There was considerable heterogeneity ($I^2 = 94\%$). The forest plot is shown in Figure 5B.

3.11 | Serum IgG levels: LNIT vs controls

Three trials assessed serum IgG as an outcome.^{14,15,35,37} In total, 79 patients were evaluated. The meta-analysis showed that the LNIT group had higher posttreatment serum IgG levels than the control group (MD, 0.45 ; 95% CI, 0.20 – 0.70 [$p = 0.0005$]). There was no heterogeneity ($I^2 = 12\%$). The forest plot is illustrated in Figure 5B.

3.12 | Nasal IgE levels: LNIT vs controls

Two trials assessed nasal-specific IgE levels as an outcome.^{34,37} Forty-six patients were investigated. The meta-analysis did not find a significant difference between the LNIT and control groups (MD, -0.59 ; 95% CI, -1.99 to 0.81 [$p = 0.41$]). Heterogeneity was absent ($I^2 = 0\%$) (Figure S7).

3.13 | Nasal eosinophil cationic protein: LNIT vs controls

Two trials assessed nasal eosinophil cationic protein (ECP) levels as an outcome.^{15,34} In total, 48 patients were examined. The meta-analysis showed no significant difference between the LNIT and control groups (MD, 7.63 ; 95% CI, -18.65 to 33.91 [$p = 0.57$]). There was moderate heterogeneity ($I^2 = 49\%$) (Figure S8).

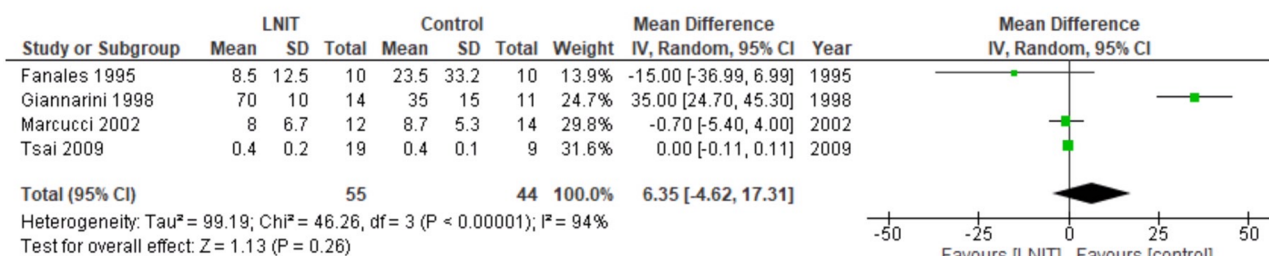
3.14 | s: LNIT vs controls

Eight trials assessed serum NPTs as an outcome.^{20–22,32,33,35,37,38,40} In all, 206 patients were involved. The meta-analysis revealed that the LNIT group had a higher NPT after treatment than the control group (MD, 27.30 ; 95% CI, 10.13 – 44.46 [$p = 0.002$]). The heterogeneity was considerable ($I^2 = 98\%$) (Figure S9).

3.14.1 | NPT subgroup analysis: NPT by age group

A subgroup analysis was performed by age group (<15 years vs ≥ 15 years). The results showed that the LNIT group had a higher posttreatment NPT than the control group for both age subgroups. There was no significant difference ($p = 0.18$) between the younger age subgroup (MD, 53.60 ; 95% CI, 15.75 – 91.45) and the older age subgroup (MD, 24.72 ; 95% CI, 6.76 – 42.68) (Figure S10).

(A)



(B)

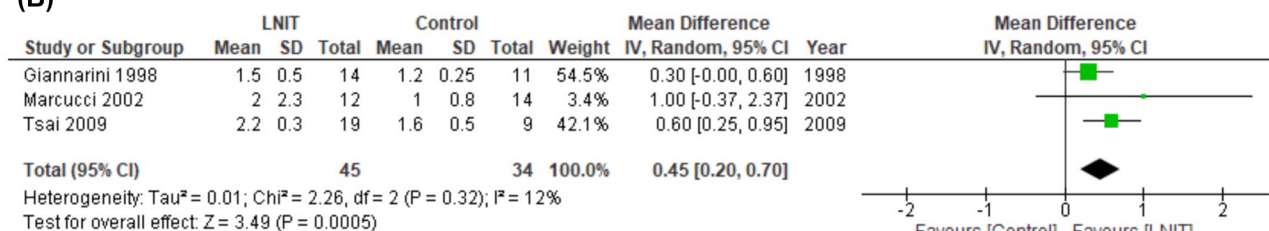


FIGURE 5 Immunologic outcome assessment. (A) Serum-specific IgE levels, (B) serum IgG levels. LNIT, local nasal immunotherapy.

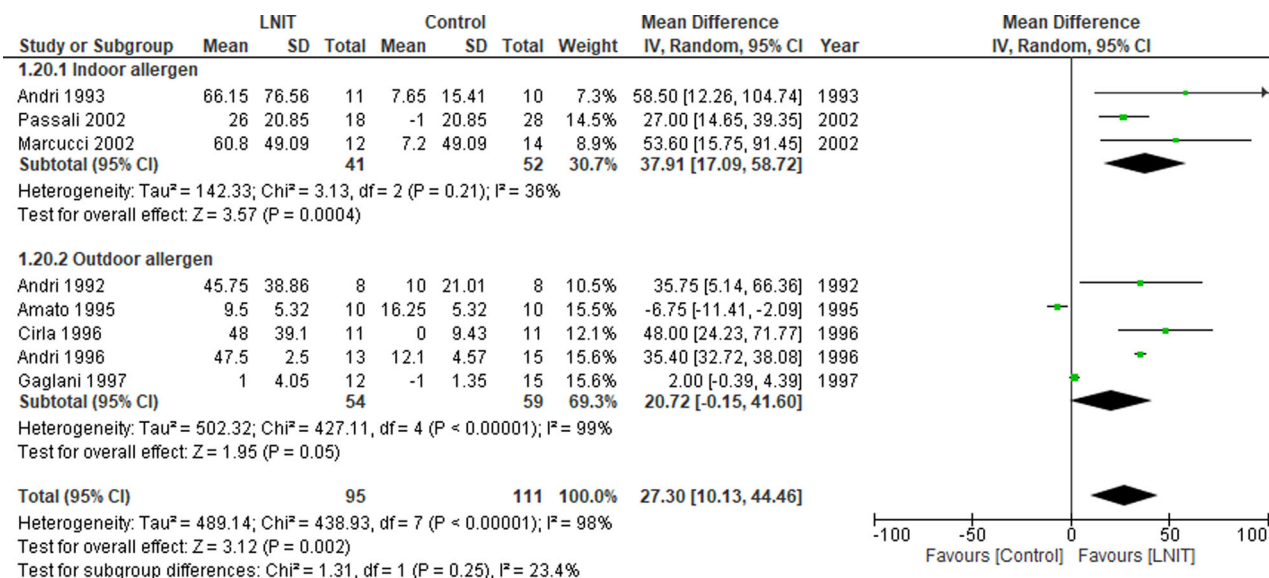


FIGURE 6 Nasal provocation threshold by allergen subtypes: local nasal immunotherapy (LNIT) vs controls.

3.14.2 | NPT subgroup analysis: NPT by allergen subtype

A subgroup analysis was performed by allergen subtype (indoor vs outdoor). The LNIT group had a higher post-treatment NPT than the control group for the indoor allergen subgroup. There was no significant difference ($p = 0.25$) between the indoor allergen subgroup (MD, 37.91; 95% CI, 17.09–58.72) and the outdoor allergen subgroup (MD, 20.72; 95% CI, -0.15 to 41.61). The forest plot is shown in Figure 6.

The summary of effects of interventions is detailed in Table 2.

3.15 | Adverse events

Regarding AEs, 12 of 14 studies reported mild local reactions: sneezing, rhinorrhea, nasal congestion, itching, and a local burning sensation. Sneezing was the most common AE. Less common were hives on the neck and watery eyes. Five studies provided raw data on AEs for the LNIT group: the mean AE rate of the group averaged 43.5% (range: 0%–100%). Only three studies provided raw data on AEs for the control group: the mean AE rate of the group was 3.12% (range: 0%–3.12%). All local AEs subsided spontaneously. No systemic AEs were reported for the adult group, and no local or systemic AEs were reported for the

TABLE 2 Summary of effects of interventions

Outcomes	Studies	Participants	SMD/MD	95% CI	I ²
TNSS ^{21,22,30,32-39}	11	298	-1.37	[-2.04 to -0.69]	84%
Nasal obstruction ^{14,15,21,30,32,36,40-42}	9	312	-0.61	[-1.06 to -0.16]	70%
Rhinorrhea ^{14,15,21,30,32,36,39-42}	10	305	-0.69	[-1.18 to -0.20]	74%
Sneezing ^{14,15,21,30,32,36,39-42}	10	300	-0.72	[-1.24 to -0.21]	76%
Itching ^{14,32,39,40}	4	98	-1.24	[-2.08 to -0.40]	69%
SMS ^{22,30,35,36,41,43}	6	165	-1.55	[-2.83 to -0.28]	90%
Medication score ^{20-22,30,32,33,36,37,40,41,44}	11	281	-1.09	[-1.35 to -0.83]	0%
Serum specific IgE level ^{14,15,34,37}	4	99	6.35	[-4.62 to 17.31]	94%
Serum IgG level ^{14,15,35,37}	3	79	0.45	[0.20 to 0.70]	12%
Nasal specific IgE level ^{34,37}	2	46	-0.59	[-1.99 to 0.81]	0%
Nasal ECP level ^{15,34}	2	48	7.63	[-18.65 to 33.91]	49%
NPT ^{20-22,32,33,35,37,38,40}	8	206	27.30	[10.13-44.46]	98%

CI, confidence interval; ECP, eosinophilic cationic protein; MD, mean difference; NPT, nasal provocation threshold; SMD, standardized mean difference; SMS, symptom-medication score; TNSS, total nasal symptom score.

TABLE 3 Summary of AEs

Authors	Local AEs			Systemic AEs
	Events	LNIT (n)	Controls (n)	
Amato et al ³³	Yes	NR	NR	No
Andri et al ²⁰	Yes	4/8	NR	No
Andri et al ²¹	Yes	4/11	1/10	No
Andri et al ³²	Yes	NR	NR	No
Bertoni et al ²²	Yes	3/9	NR	No
Cirla et al ⁴⁰	Yes	9/11	NR	No
Gaglani et al ³⁵	Yes	2/12	NR	No
Georgitis et al ³⁶	Yes	NR	NR	No
Georgitis et al ⁴¹	Yes	NR	NR	No
Marcucci et al ³⁷	No	0/12	0/14	No
Nickelsen et al ³⁰	Yes	15/15	NR	No
Passalacqua et al ⁴³	No	0/7	0/8	No
Passali et al ³⁸	Yes	NR	NR	No
Welsh et al ³⁹	Yes	NR	NR	No

AEs, adverse events; LNIT, local nasal immunotherapy; NR, not reported.

pediatric subgroup. There was limited detailed information from the original articles in part of AEs; thus, we could not report the data of the specific AEs such as rhinorrhea or itching. The AEs are detailed in Table 3.

4 | DISCUSSION

This systematic review and meta-analysis of LNIT considered 20 studies with 698 participants. The results showed positive effects of LNIT on TNSS and all symptom scores, including nasal obstruction, the most difficult to treat symptom. The itching symptom score demonstrated the highest degree of improvement, followed by sneezing,

rhinorrhea, and nasal obstruction. TNSS (SMD, -1.37; 95% CI, -2.04 to -0.69) and itching symptom score (SMD, -1.24; 95% CI, -2.08 to -0.40) not only provided statistical significance but also demonstrated clinical significance with a magnitude of SMD >0.8.⁴⁵ To our knowledge, this is the first meta-analysis of LNIT. However, there was a qualitative systematic review on this topic by Passalacqua et al in 2006.¹⁶ All 21 trials in the work by Passalacqua et al were assessed in our review.

Current guidelines and recommendations on AR mostly mention SCIT and SLIT.⁴⁶ LNIT and other routes are presented only as options and with limited information. A meta-analysis by Huang et al⁸ reported no significant difference in the symptom scores of SCIT and SLIT. The

effectiveness of SCIT and SLIT was demonstrated in a recent meta-analysis. Relative to placebo, the SMD of TNSS for SLIT was -0.33 (95% CI, -0.54 to -0.13),⁷ while for SCIT the SMD was -2.17 (95% CI, -3.50 to -0.84).⁸ In our work, the effect of LNIT on TNSS was comparable to those of both conventional methods. In a comparison between LNIT and SCIT, a randomized controlled trial by Giannarini et al¹⁴ showed no significant difference in the symptom scores of the two groups.

The subgroup analysis of TNSS by age (<15 vs ≥ 15 years) showed a significant difference in favor of the younger age group. This finding is consistent with a study comparing the efficacy of SCIT for pediatric and adult patients with AR. The results demonstrated better symptom scores and better combined medication scores for children than adults.⁴⁷ Two reasons are possible. First, the pediatric participants had smaller nasal cavities than the adult participants. This characteristic led to a higher degree of distribution of the topical solution on the intranasal surface area. Moreover, the smaller nasal volume resulted in more concentrated, and therefore more potent, local medication for the children than the adults. Second, the pediatric immune response is more active than the adult immune response. This difference was identified by a study of AEs related to current SCIT practices, which reported a higher systemic reaction rate among children.⁴⁸

All of the articles evaluated the effect of immunotherapy for outdoor allergens—applied immunotherapy during the preseasonal period to enable adequate duration for optimal response at the peak-pollen period. The LNIT group had a more favorable TNSS than the control group for the outdoor allergen subgroups during the peak pollen assessment. A future study evaluating the effect of immunotherapy delivery timing of seasonal allergens comparing preseasonal, in-seasonal, and postseasonal is recommended.

Different allergen formulations were used in LNIT studies. In the past, the stability of liquid allergens and the control of the dosage of aqueous allergen preparations were problematic. These shortcomings led to the development of a lyophilized, macronized allergen powder.³⁷ Nevertheless, there was no difference in the improvement in the TNSS obtained with the powder and aqueous forms.

Decreasing medication usage is another goal of AIT. In 2007, the World Allergy Organization defined the need for rescue medications as primary end point parameters in clinical outcome measures: one point for oral or intranasal antihistamines, two points for nasal corticosteroids, and three points for oral corticosteroids.⁴⁹ Although all of the studies in our review were published before the proposal for a standardized scoring system, the results still revealed a decline in medication usage.

The immunological assessments demonstrated an increase in serum IgG in the LNIT group. Surprisingly, no difference in serum-specific IgE was evident after treatment. The timing of serum-specific IgE measurements may be too early to detect changes. Two of four studies assessed serum-specific IgE at 10 to 16 weeks,^{15,34} while it was evidenced to decrease at 6 to 12 months.⁵⁰ Nasal-specific IgE and ECP showed similar effects in the LNIT and control groups. This result was counter to what was expected from the local immune response in NALT. Several factors can explain inaccurate measurements, including nasal secretion collection techniques, dilutional effects by mucosal secretions, and the effects of mucociliary clearance. Furthermore, the timing of the specimen collections in both included studies for nasal ECP was too early.

The NPT was higher for the LNIT group after treatment. This result supports the principle of LNIT, which directly triggers immunomodulation in NALT. Although NPT is used primarily in research rather than in everyday clinical practice,⁵¹ it is a valuable test for assessing the response from LNIT. There was no significant difference between the indoor and outdoor allergen subgroups. However, the indoor allergen subgroup tended to have a more noticeable improvement.

Forty-three percent of the participants in the LNIT group experienced local reactions, such as sneezing, mild rhinorrhea, nasal congestion, itching, and a local burning sensation. This rate was comparable with local reactions caused by SLIT (39%–47%).^{52,53} Nickelsen et al^{30,31} and Cirla et al⁴⁰ reported a high incidence of local AEs. This high incidence could be attributable to the variation of the report degree accepted by each article without the same report standard. No systemic reaction was reported from any of the included studies in LNIT, unlike SCIT, in which systemic side effects were reported to be up to 7%.⁸

The limitations of this meta-analysis are the high risk of bias, the presence of publication bias and the high heterogeneity of the included studies. According to the favorable outcomes of LNIT and the advancement of the biomedical technique of product development (eg, liposomal nanotechnology for drug carriers), LNIT could be an excellent alternative immunotherapy application route for patients with AR. Further research assessing the immunologic outcome with a more extended follow-up period and drug delivery technique is recommended.

5 | CONCLUSIONS

LNIT is an alternative route for noninjection immunotherapy. The current meta-analysis supports the efficacy and safety of LNIT. There are benefits of LNIT in symptom reduction and decreased medication use. TNSS and all

symptom scores (including nasal obstruction, rhinorrhea, sneezing, and itching) were lower for the LNIT group than for the placebo group. The SMS and medication score also decreased in the active treatment group. The NPT after LNIT increased significantly. Last, no serious AEs were reported.

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CONFLICT OF INTEREST

The authors have no financial relationships or conflicts of interest to disclose

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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