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ORIGINAL ARTICLE



Sublingual immunotherapy in patients with latex allergy: systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Latex allergy (LA) is a commonly observed entity for which sublingual immunotherapy (SLIT) has been shown to be effective in many small randomized clinical trials. The present study was conducted with an aim of systematically reviewing the existing literature on the efficacy and safety of SLIT in patients with LA and to apply the principles of meta-analysis. A search for randomized controlled trials with appropriate search strategy in PubMed and CENTRAL was conducted. Studies with documented clinical history of LA and SLIT administered in any dose, duration and regimen compared with placebo were included. Outcome measures were symptom scores, glove provocation test score, serum IgE levels, induration following latex skin prick test, medication scores and adverse effects. Random effects model was used when moderate to severe heterogeneity was observed and fixed effects model when there was mild heterogeneity. Forest plots for standardized mean difference (95% confidence interval) for all the continuous outcome measures were created. A total of 152 records were identified from the electronic databases and four studies were finally included in the meta-analysis. A statistically significant reduction for induration following glove provocation test (pooled results from two studies) was observed in the SLIT group with SMD of -0.9 [-1.71 , -0.08]. No significant differences were observed in any other outcome measures between the interventions. We did not identify significant reduction in most of the outcome measures with SLIT in patients with LA except for glove provocation test score wherein only two studies were included. Large and more randomized controlled trials are required to ascertain and confirm the utility of SLIT in such patients.

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KEYWORDS

SLIT; immunotherapy;
desensitization

Introduction

IgE-mediated allergy to latex proteins, found in the sap of *Hevea brasiliensis*, is common not only affecting the healthcare workers but also hairdressers, food handlers, cleaners, construction workers, green house workers and general public (1,2). A prevalence of 5–16% for latex allergy (LA) was observed across much population (3–5). A higher prevalence of LA (50%) was observed in patients with spina bifida (6). A total of 14 antigenic proteins have been identified in the sap of *Hevea brasiliensis* that may act as allergens in humans (7). Latex is being used in the manufacture of gloves, condoms and balloons. In the pandemic era of infections by human immunodeficiency virus and hepatitis B virus, the use of gloves has increased several folds amongst healthcare personnel and so the prevalence of LA. Similarly, patients with spina bifida also get repeated exposure to latex and so are more susceptible to LA (8). Additionally, some patients develop secondary sensitivity to latex following the use of plant-foods such as banana, the constellation of symptoms and signs being named as *latex-fruit syndrome* (9).

LA with anaphylaxis, especially in pregnant during labor and delivery may pose complications (10). In a review by United States Food and Drug Administration analysis, 79% of the hypersensitivity reactions were reported to occur due to use of latex containing gloves (11). Avoiding contact with latex containing products is the best and initial measures to be considered for patients with

LA (12). However, individuals with LA in professions requiring frequent encounter with latex can be treated either symptomatically with drug therapy that temporarily reduces the symptoms or desensitization with immunotherapy that lasts longer. Immunotherapy with the most crucial latex allergens administered either subcutaneously or sublingually forms the mainstay of desensitization in patients with LA. Subcutaneous immunotherapy is administered in a hospital setting by trained personnel backed up with all the resuscitative measures for handling emergency. In fact, subcutaneous immunotherapy was first introduced and was found to be highly effective but has a drawback of causing serious adverse drug reactions and has to be given in allergists' office (13). Later, sublingual immunotherapy (SLIT) was introduced (14) and has been well evaluated in patients with allergic rhinitis, conjunctivitis, allergic rhinitis and bronchial asthma with promising results (15,16). Considering the absence of any systematic review on the utility of SLIT in patients with LA, the present study was carried out.

Methods

Information sources and search strategy

The protocol for this review was registered with International prospective register of systematic reviews (PROSPERO) with the registration number CRD42015027191. A thorough literature search

was conducted and was completed on 2 September 2016. The primary database used was Medline (via PubMed) and Cochrane central register of clinical trials (CENTRAL). The keywords applied for the search were latex [tiab] AND immunotherapy [tiab]. Additionally, trial registries such as World Health Organization and Clinical Trials.gov were searched for the appropriate studies. This search was further supplemented by hand searching of references from the published literature and the relevant authors were contacted in case of any clarifications. No limits were applied regarding year of the study or language.

Eligibility criteria

Only those studies with randomized and placebo controlled design with the following requirements were included in the present study:

1. *Type of participants* – Patients with documented clinical history of LA manifesting in the form of either urticaria or asthma or conjunctivitis or rhinitis with a positive latex skin prick test.
2. *Type of intervention* – Sublingual immunotherapy in any dose, duration and regimen.
3. *Comparison* – Placebo.
4. *Outcome* – The primary outcome measures were the symptom scores (total, rhinitis, conjunctivitis and asthma scores) and glove provocation test score. The secondary outcome measures analysed in the study included serum IgE levels, induration following latex skin prick test, medication scores and adverse effects. We looked at the details of the entire above mentioned outcome measures between the study groups at 3, 6 and 12 months.

Study procedure

Both the authors of this study individually screened the above mentioned databases for studies and independently reviewed abstracts for suitability. Full-text articles were obtained for those found to be eligible and those that were inconclusive on the abstract screening. A pre-tested data extraction form was created and both the authors independently extracted the following data from each eligible study: trial site, year, trial methods, participants, interventions and outcomes. Disagreement between the authors was resolved through discussion. The extracted data were analyzed using RevMan 5.3 software. The methodological quality of eligible trials was independently assessed by both the authors using The Cochrane collaboration's tool for assessing the risk of bias and Jadad's scale (17,18). We followed the guidance to assess whether trials took adequate steps to reduce the risk of bias across six domains: sequence generation, allocation concealment, blinding (of participants, personnel and outcome assessors), incomplete outcome data and selective outcome reporting. The judgment was categorized into low, high or unclear risk of bias. Standardized mean difference for all the continuous outcome measures was compared between the treatment groups using Forest plot, when more than one study was found to be eligible for that outcome and relative risk for adverse outcomes. The heterogeneity between the studies was assessed using the Forest plot visually, I^2 statistics wherein more than 50% was considered to have moderate to severe heterogeneity and Chi-square test with a statistical p value of less than .10 indicates statistical significance and random-effect models were used. In case of mild heterogeneity, fixed-effect model was used for analysis. Considering the presence of very few trials that can be included in the review, publication bias could not be assessed. The present meta-analysis

was conducted and presented in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (19).

Results

A total of 137 records were identified from PubMed and 15 from CENTRAL. Figure 1 depicts the PRISMA flowchart on the search results of the present review. Four studies (20–23) were finally included in the meta-analysis and their characteristics are reported in Table 1. None of the eligible studies reported allocation concealment and three out of five studies did not report the generation of random sequence. A summary of risk of bias of the included studies is depicted in Figure 2.

Symptom scores

Only one (20) of the four eligible studies with a total of nine patients compared the effect of SLIT with placebo on the total symptom scores as well as rhinitis, asthma and cutaneous scores. The standardized mean difference [95% CI] was observed to be $-1.39 [-2.96, 0.18]$, $-1.63 [-3.29, 0.02]$, $-2.44 [-4.44, -0.45]$ and $-1.61 [-3.26, 0.03]$, respectively, with a statistical significance observed only with the asthma scores. None of the included studies reported conjunctivitis score.

Glove provocation test score

One of the eligible studies (20) had compared the induration following glove provocation test at 6 months between SLIT and placebo groups with a total of nine patients and the standardized mean difference [95% CI] was estimated as $-1.09 [-2.57, 0.38]$. Similarly, two studies (20,23) with a total of 29 patients had assessed the same at 12 months and the Forest plot for the outcome measure is depicted in Figure 3. A statistically significant reduction in the induration was observed at 12 months with SLIT.

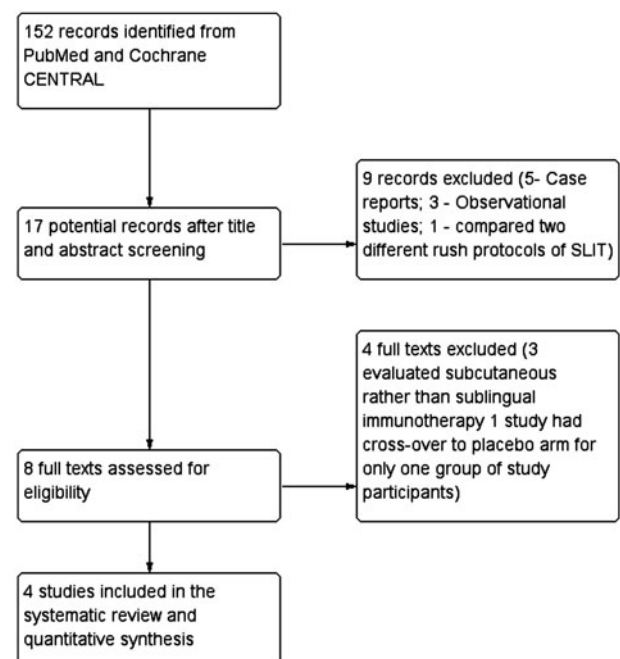


Figure 1. PRISMA study flowchart.

Table 1. Comparison of the profiles of the studies included in this review.

Study ID	Country	Jadad's score	Patients	Interventions	Outcomes considered in the study	Dropouts/withdrawals and reported adverse events
Buyukozturk 2010 (20)	Turkey	4	Diagnosed as LA by clinical history, positive latex prick test, latex glove provocation test and latex specific IgE antibody. Mean (range) age of the study participants was 28.7 (26–32) years with male:female ratio of 1:7 and 1:3 in SLIT and placebo groups, respectively. All the study participants were healthcare workers. A total of eight and four participants were recruited in the SLIT and placebo arms, respectively.	Four day induction and 12 day maintenance dose with the total dose of 1005 µg of SLIT were administered to one group of study participants and placebo to another group.	General symptom score, glove use provocation test score, serum IgE levels, latex skin prick test and adverse events were reported at baseline, 6 and 12 months.	Three participants in the SLIT were dropped out from the study due to serious systemic reactions such as acute flushing, itching, rhinitis, conjunctivitis, wheeze, dyspnea, chest tightness and hypotension.
Nettis 2007 (21)	Italy	4	Diagnosed as LA with clinical history such as urticarial or asthma following contact with latex and positive to either glove use test or latex bronchial provocation test. Mean (range) age of the study participants was 38.1 (18–47) years with male:female ratio of 1:2 in SLIT and 1:3 in placebo group. A total of 20 participants were recruited in each group.	SLIT was administered at a total dose of 1002.2 µg in a 4 day induction period and 12 month maintenance and placebo was administered to another group.	General symptom score, glove use provocation test score, serum IgE levels, latex skin prick test and adverse events were assessed at baseline and 12 months. Additionally, skin prick test was carried out at 6 months.	Two participants in the SLIT and three in placebo group discontinued treatment due to noncompliance ($n = 3$), inefficacy ($n = 1$) and change of residence ($n = 1$). A total of 3/18 in SLIT and 1/17 in placebo arm developed systemic reactions.
Nettis 2010 (22)	Italy	5	Diagnosed as LA by clinical history, positive to skin prick test and serum specific IgE antibodies. A total of 12 and nine participants in SLIT and placebo arm, respectively, were recruited with a mean (range) of age of 34.3 (20–46) and 36.8 (22–49) years and male:female ratio of 1:3 and 1:8, respectively.	SLIT was administered at a total dose of 591.2 µg over a period of 3 days and an identical placebo preparation in terms of presentation, taste and color was administered to another group of study participants.	Adverse events	No drop-out or withdrawal from the study. One in the SLIT and three in the placebo groups developed systemic adverse reactions.
Bernardini 2006 (23)	Italy	5	Children with clinical signs of allergy to natural rubber latex with mean (range) ages of 10.3 (5–14) and 11 (5–14) years in SLIT and placebo groups, respectively, were recruited. A total of 12 participants in SLIT and eight in placebo group with male:female ratio of 2:1 and 1:1, respectively.	SLIT was administered at a total dose of 902.2 µg over a period of 4 days followed by a maintenance schedule for a period of 12 months. Placebo was administered to the comparator group.	General symptom score, glove use provocation test score, serum IgE levels, latex skin prick test and adverse events were recorded at baseline and at the end of one year of treatment.	None of the study participants had any local or systemic adverse reactions.

Serum IgE levels and induration following latex skin prick test

Only one of the eligible studies (23) with a total of 20 patients reporting the changes in serum IgE levels at 12 months was analyzed and the standardized mean difference [95% CI] was found out to be 0.47 [−0.14, 1.09]. Similarly, the same study (23) assessed the induration following latex skin prick test at 12 months and the standardized mean difference [95% CI] was

observed to be −0.43 [−1.05, 0.18] and was not statistically significant.

Adverse effects

All the studies (20–23) reported adverse events in both the groups. Figure 4 depicts the Forest plot of adverse events and the pooled risk ratio was not significantly different for SLIT group. The details of the reported adverse events are mentioned in Table 1.

Discussion

We undertook the present systematic review and quantitative analysis to identify the clinical efficacy of SLIT in patients with LA. Five eligible studies were identified with a total of 116 patients. A statistically significant reduction in induration following glove provocation test was observed with SLIT while no statistically significant difference was observed for all other outcome measures with SLIT in comparison with placebo.

SLIT can be administered either as sublingual spit or swallow, of which the latter has been shown to be more preferable (24). Considerable variations in the dose and regimen have been observed in the literature (25). This was also evident in the present review but we could not perform any sub-group analysis due to limited eligible studies. Further studies are definitely mandatory for optimizing treatment outcomes. Hospital healthcare workers will be required to use gloves often and allergy to latex would definitely be a major problem of this cohort. Of the four eligible studies in the present review, only one (20) included healthcare workers as study participants.

We did not observe increased risk of adverse events with SLIT in comparison with placebo use in the present review. In fact, SLIT has been shown to be safe with only few incidences of adverse reactions reported from all the studies. The local side effects following SLIT has been observed to be prevalent to an extent of around 40–85% from various clinical trials (26). Recently, more specific latex allergens have been used for immunotherapy with reduced potential for inducing allergic reactions. Although serious systemic reactions have been observed, none of the

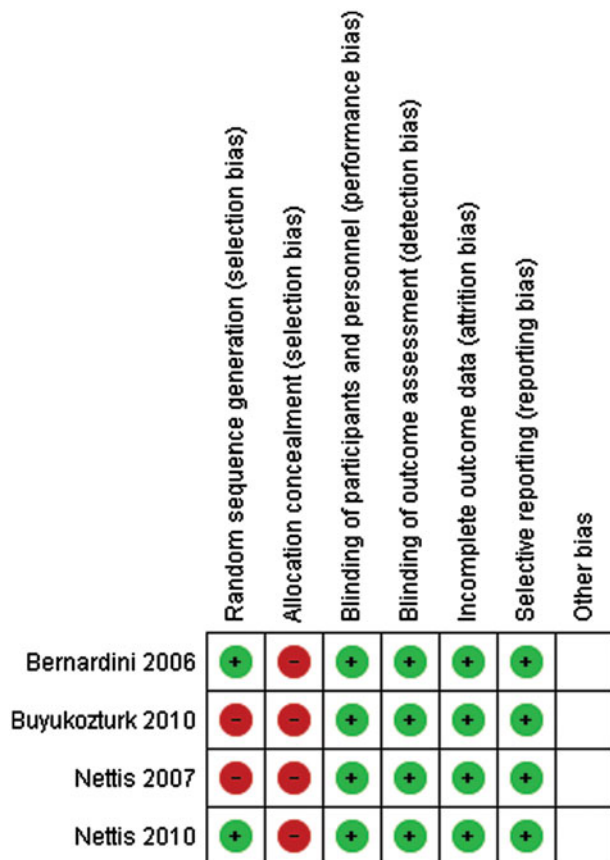


Figure 2. Risk of bias graph.

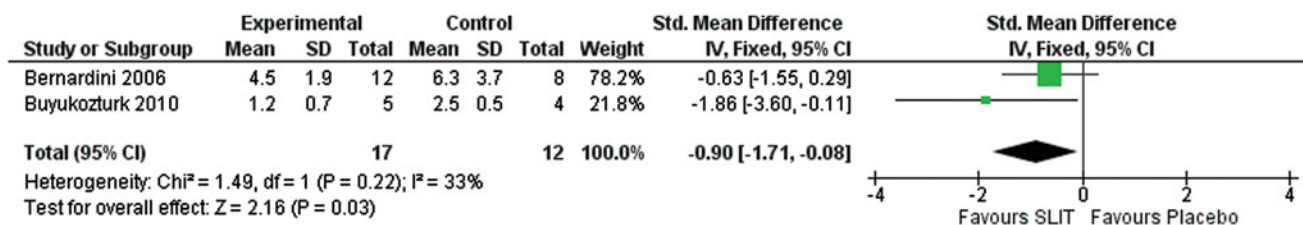


Figure 3. Forest plot for induration following glove provocation test at 12 months between the interventions.

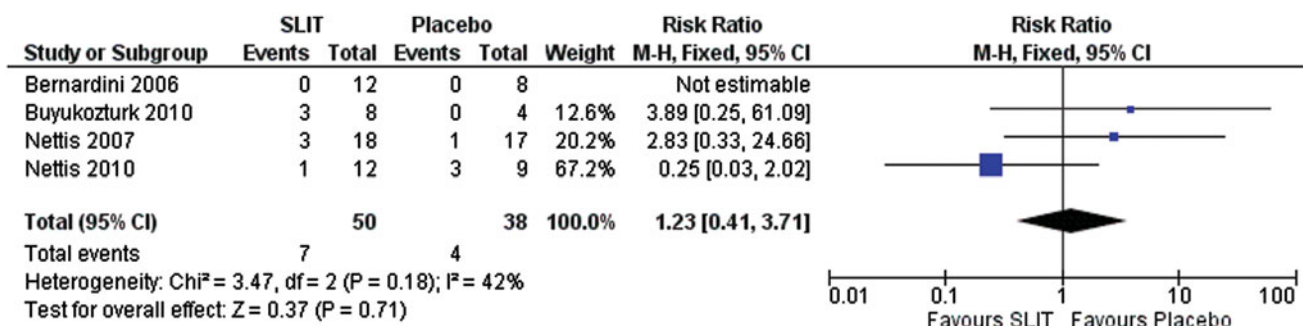


Figure 4. Forest plot of adverse events with SLIT in comparison to placebo group.

studies reported death due to SLIT use in patients with LA. In fact, studies have confirmed long term safety (3–8 years) of SLIT in patients with LA (27). The huge benefit of desensitization that lasts longer clearly outweighs the risk of adverse events associated with SLIT and so should not be a factor limiting its preference for patients with LA. Also, a joint task force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology's Immunotherapy and Allergy Diagnostic Committees critically appraised the existing literature and concluded that cost-benefit calculations could not be performed for SLIT in LA due to absence of concrete evidence (28). However, Berto et al. (29) did analysis of SLIT in patients with pollen allergy and found it to be more cost effective than using symptomatic drug treatment. Several such studies are required from different parts of the world for prudent evidence on cost utility of SLIT in patients with LA.

Recently, World Allergy Association has classified Hev b 1, 3, 5 and 6 to be genuine latex allergens and positive test to any of these allergens should be a warning in order to use appropriate safety measures (30). In fact, it has been reported that patients who have undergone multiple surgeries and health care workers exhibit variation in the type of latex allergens attributed to the side of gloves to which they have been exposed (31). Interestingly, the above said four latex allergens have been shown to be extracted from latex gloves and subsequently used for either diagnosis or immunotherapy of LA (32). Dexamethasone treated dendritic cells have been shown to restore tolerance to LA in humans *in vitro* (33). However, more *in vivo* studies are required for placing more reliability on the utility of the same.

SLIT can be considered for the management of LA from other individual observational and interventional studies, albeit in the present meta-analysis where a statistically significant difference was observed only with glove provocation test. Also reports exist related to its failure in some patients, the only other measure is to use products made of synthetic elastomers. The strength of the present analysis includes the assessment of interventions on the clinically important outcome measures (34) while seriously limited largely by the underpowered studies and inconsistencies in reporting various scoring systems and objective measures of allergic reactions which should be taken care of by the investigators in future studies in order to facilitate quantitative synthesis. To conclude, we found a statistically significant improvement in glove provocation test score with SLIT suggestive of beneficial effect in patients with LA. However, large randomized controlled trials with adequate randomization techniques including appropriate concealment of allocation and reporting of outcome measurements using standardized symptom scales are required to confirm the clinical utility of SLIT in such patients.

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Disclosure statement

The authors declare that they have no conflict of interest.

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