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Internal Medicine Section

A Prospective Quasi-Experimental Study on the Effect of Sub-Lingual Immunotherapy with Multiple Allergens in Allergic Bronchial Asthma

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ABSTRACT

Background: Sub-lingual immunotherapy (SLIT) has been introduced as a disease modifying agent for allergic bronchial asthma in many countries and currently practicing in India.

Aims: To assess the outcome of adding multiple-allergen sub-lingual immunotherapy with rescue medicines in patients having allergic bronchial asthma and to document adverse events, if any.

Settings and Design: This was a clinic-based prospective quasi-experimental study.

Methods and Material: Patients giving consent to receive multiple-allergen SLIT and rescue medicines formed the experimental group (Group A) while patients who did not give consent to SLIT but wished to have only rescue medicines formed the comparison group (Group B). Follow-up was done up to three years. Initially 703 patients were in Group A and 313 in Group B. However, around 647 patients in Group A and 282 in Group B completed the study for three years.

Statistical Analysis: Unpaired t- test was used to compare the difference between the mean symptom and medication scores in Group A and Group B, before intervention and at the end of the study. Paired t- test was applied to compare the mean scores before and after intervention for each group separately.

Results: Mean symptom scores of the two groups did not vary significantly before intervention but found to be significant at the end third year [8.60 (SD 3.92) v 14.73 (SD 4.42), P<0.001). In both groups mean symptom scores decreased from the baseline but it differed significantly in Group A only [15.46 (SD 4.88) v 8.60 (SD 3.92), P<0.001]. The mean medication scores between the two groups also differed significantly at the end of the third year [1.60 (SD 0.31) v 2.98 (SD 0.44), P<0.001)]. The scores also decreased in both the groups from the baseline, but significantly only in Group A [3.10 (SD 0.50) v 1.60 (SD 0.31), P<0.001]. Around 6.4% (45/703) patients receiving SLIT complained of mouth and throat irritation and about 3.7% (26/703) complained of mild vomiting. It can be concluded that long term sub-lingual immunotherapy in addition to rescue medicines significantly improves both symptom and medication scores with a high degree of safety.

Key Words: Allergic asthma, sub-lingual immunotherapy (SLIT), quasi-experimental study

INTRODUCTION

Bronchial Asthma is a serious public health problem throughout the world, which are affecting people of all age groups. Uncontrolled asthma affects normal daily activities severely and fatality is often reported [1].

It is a chronic inflammatory disorder of the airways which become hyper-responsive. On exposure to various risk factors, they get obstructed by narrowing, increased inflammation and accumulation of mucus plugs [2]. Among the common risk factors, exposure to allergens like house dust mites, fur of animals, pollen and others play a major role in the development bronchial hypersensitivity [2].

As inflammation, involving various cells, cytokines and mediators like leukotrienes, plays the central role in the pathogenesis of asthma, inhaled corticosteroids are the mainstay of asthma treatment [1, 3]. However, specific immunotherapy is the only treatment capable of modifying the response to allergens at the very early stages of immune response, and thereby restoring the imbalance between type 1 helper (TH1) and type 2 helper (TH2) lymphocyte subsets [4]. In recent years, the sub-lingual administration of immunotherapy (SLIT) has gained increasing credibility, and is now included in guidelines [5]. SLIT, like any other specific immunotherapy, has been found to cause down regulation of the inflammatory process in the target organs during exposure to allergens [6-8] and also reduce bronchial hyper-responsiveness to a great extent [9-11]. The main advantages of SLIT are self-administration at home and the favorable safety profile in children as well as in adults [12, 13]. SLIT is now used in many European countries [3] and USA [14] and currently is in practice in India. But literature is scarce regarding the efficacy of multiple-allergen SLIT in bronchial asthma in Indian subcontinent.

Hence the aim of the present study was to assess the outcome of adding multiple-allergen sub-lingual immunotherapy with rescue medicines in patients having allergic bronchial asthma and to document adverse events, if any.

MATERIALS AND METHODS

Selection of Study Participants

All patients aged between five to thirty five years, who were reported with the symptoms of asthma at the Allergy, Asthma and Chronic Obstructive Pulmonary Diseases (COPD) unit at Lifestyle Clinic in Kolkata, West Bengal, India, were subjected to thorough physical check up (after taking proper clinical history, family history

and environmental history), pulmonary function test (PFT), sputum smear microscopy for acid fast bacillus (AFB) and chest x-ray. Patients found to be suffering from bronchial asthma (based on pre- and post-dilatation PFT results), were further subjected to modified skin prick test (taking proper precautions), enzyme- linked immuno-absorbent assay (ELISA) for specific immunoglobulin E (IgE) and total IgE and bronchial provocation test with histamine. Patients with cardiovascular and other serious co-morbidities and those who were pregnant were excluded from the study. In this way a total of 1016 patients were found to be suffering from allergic bronchial asthma. All of them were informed regarding possible benefits and uncertainties of SLIT and the nature of the study and provided with option of undergoing SLIT in addition to rescue medicines with inhalational bronchodilators and corticosteroids as per individual patient's need. Altogether 703 consent from Pateints for SLIT and were included in the study group (Group A). The remaining 313 who did not give consent for SLIT but wished to receive rescue medicines were included in the comparison group (Group B). However, a total of 647 patients in Group A and 282 in Group B completed the study for three years and were included in the final analysis.

Study Design

This was a prospective quasi-experimental study with a three-year follow-up (from October 2008 to September 2011). Patients receiving SLIT and rescue medicines formed the experimental group (Group A) while patients receiving only rescue medicines formed the comparison group (Group B). Harris D et al, in a systematic review, discussed at length about the advantages and disadvantages of quasi-experimental studies and concluded that if performed meticulously such type of study could make significant contribution [15]. Quasi-experimental (sometimes called pre-post intervention) studies encompass a broad range of non-randomized intervention studies. Evidences from these kinds of studies are of course inferior to those obtained from double blinded, placebo controlled, randomized trials, but these designs are frequently used when it is not logistically feasible or ethical to conduct a randomized controlled trial. The increasing capacity of health care institutions to collect routine clinical data has led to the growing use of quasi-experimental study designs in the field of medical informatics as well as in other medical disciplines [15]. The present researchers, instead of using a more conventional study design like randomized controlled trial (RCT), chose to conduct a quasi-experimental design because SLIT was already in practice in India and conducting a RCT raised certain ethical issues regarding randomization, availability of a suitable placebo, and patients' benefits and possible risks. Under these circumstances the present study design was selected being fully aware of the limitations like non-randomization, selection and subjective bias, and weakness in proving causality through statistical associations.

Ethical Consideration

Ethical clearance and approval to conduct the study was obtained from the ethical committees of Mata Gujri Memorial Medical College and L.S.K. Hospital, Kishanganj, Bihar, India and Lifestyle Clinic, Kolkata, West Bengal, India. Written informed consent was obtained from all the participants.

Symptom and Medication Scores

The symptoms like breathlessness (confirmed by PFT), persistent cough (night cough), wheezing, nasal blockage (or running nose), repeated sneezing were scored from zero (absent) to three (severe). Other allergic manifestations like urticaria and conjunctivitis were also scored similarly. Total symptom score thus ranged from zero to twenty one.

Medication score was calculated in the following way:

- No medication required currently = zero
- Daily dose of inhalational formoterol and budesonide = one, with
- S.O.S dose of Inhalational levo-salbutamol, occasionally = two, or
- S.O.S dose of Inhalational levo-salbutamol, daily for less than a week = three, or
- S.O.S dose of Inhalational levo-salbutamol, daily for more than a week = four
- Total medication score ranged from zero to four.

Baseline data were collected before intervention from both the groups and symptom and medication scores were calculated at the beginning of the study and during each follow-up for both the groups.

Treatment Protocol

The materials for SLIT were procured from Creative Diagnostic Medicare Private Limited, Vashi, Navi Mumbai, India (www.creativedrugindia.com). Allergens with positive reaction equivalent to histamine (positive control) and glycerinated normal saline (negative control) were taken. Glycerinated aqueous allergenic extract for specific immunotherapy consist of major allergens as determined by the sensitivity (modified skin test). Composition of allergens was determined by patient's individual sensitivity spectrum. Then each treatment was individually formulated. The extract suspended in extracting fluid (Coca's solution), containing 50% glycerin I.P. was standardized to weight by volume (w/v) ratio of native materials to the extracting fluid. Each course was provided in multi-dose vial of allergens with colour coded in graded strength given below:

Treatment set: Vial 1 (black)-0.01% w/v
Vial 2 (green)-0.1% w/v
Vial 3 (blue)-1% w/v
Maintenance set – 1% w/v

Maintenance dose was continued for three years. Dosage patterns where advised according to patient's sensitivity & tolerance.

Composition of SLIT: Glycerin aqueous extract consists of concentration 100 times of the dose administered in sub-cutaneous immunotherapy (SCIT). Doses were prescribed in the form of drops. Drops were advised to be taken daily at same time in empty stomach. No food was allowed after at least for half an hour after taking SLIT. Drops were kept for five minutes sublingually then swallowed with half a cup of cool water.

Dosages were scheduled in the following way:

	1st day	3rd day	6th day	8th day	10th day	Subsequent
1st vial (0.01 w/v)	2drops	4drops	6drops	8drops	10drops	10 drops
2nd vial (0.1 w/v)	2drops	4drops	6drops	8drops	10drops	10 drops
3rd vial (1 w/v)	2drops	4drops	6drops	8drops	10drops	10 drops

Maintenance dose was the Top Tolerable Dose of the third vial up to three years as per schedule. When there was interruption of more than four weeks the therapy was resumed from the initial dose. In case interruption for two to less than four weeks therapy was re-instituted with half of the dose last given, considering safety of the patients.

Both the groups were prescribed as a combination of inhalational long acting bronchodilator (formoterol) and inhalational corticosteroid (budesonide), and inhalational short acting bronchodilator (levo-salbutamol) as rescue medicine as per individual patient requirement, anytime during the entire study period. All patients in both the groups received influenza vaccine (Influvac) each year as per guidelines [1]. All were advised to fill up the symptom and treatment diaries provided to them during the entire study period. Patients were informed regarding the importance of adherence to therapy and regular follow-up. They were also advised to contact with the principal investigator in case of emergency.

Follow-Up

Follow-up for review of treatment outcomes in both the groups were carried out at the pre-scheduled intervals. Symptoms and treatment diaries were checked and any incidence of adverse reaction was noted. Follow-up investigations included thorough physical examination, PFT and modified skin prick test.

STATISTICAL ANALYSIS

SPSS 10 was used for statistical analysis. Unpaired t-test was done to compare the difference between the mean symptom and medication scores in Group A and Group B, before intervention and at the end of the study at 36th month. Paired t-test was applied to compare the mean scores before and after intervention for each group separately.

RESULTS

About 51.5% (478/929) of the study subjects belonged to 15 to 24 years age group, 38.2% (355/929) were in 25 to 34 years and 10.3% 96/929) in 5 to 14 years of age group. There was no significant difference between the mean age of Group A and Group B [23.80 (SD 10.80) v 22.60 (SD 13.50), t (927) = 1.44, P = 0.150]. Around 54.0% (502/929) were males and 46.0% (427/929) were females. About 62.1% (577/929) were from urban areas and 37.9% (352/929) came from rural areas. Around 36.5% (339/929) and 24.3% (226/929) had exposure to dust and dampness respectively at home and 28.1% (261/929) were exposed to both. It was also observed that about 80% (742/929) of the study subjects had a family history of allergic disorder among first degree relatives.

Breathlessness (89.4%), nasal blockage (70.5%) and repeated sneezing (70.5%) were the most common symptoms among the study subjects [Table/Fig-1]. Polyvalent house dust (95.1%) was found to be the commonest type of allergen. Other common allergens which was found were pollen (74.8%), food (62.3%), mites (33.3%) and fungi (23.6%) [Table/Fig-2]. Commonest pollens were Cynodon Dactylon, Cocos Nucifera, Peltophorum Pterocarpum, and Azadirachta Indica (not shown in table).

Symptoms	Percentage
Breathlessness	89.4
Persistent cough (night cough)	39.7
Wheeze	46.2
Nasal blockage (or running nose)	61.3
Repeated sneezing	70.5
Urticaria	12.2
Allergic conjunctivitis	3.3

[Table/Fig-1]: Symptoms among the study subjects (n = 929)*
*Multiple responses.

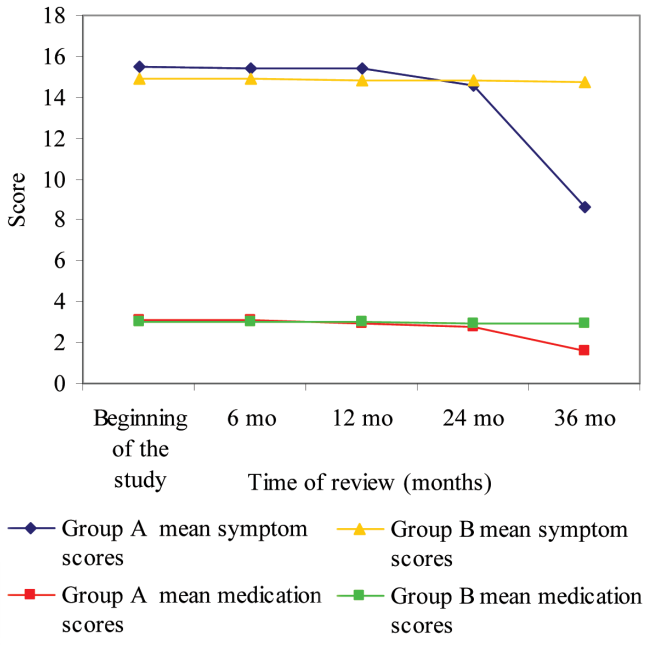
Allergen	Percentage
Polyvalent house dust	95.1
Mites	33.3
Pollen	74.8
Fungi	23.6
Dander	1.4
Insect	2.1
Food	62.3

[Table/Fig-2]: Types of allergen found among the study subjects (n = 929)*
* Multiple allergens

Period of review	Mean symptom score and standard deviation		Unpaired t- test
	Group A (n = 647)	Group B (n = 282)	
Before intervention	15.46 (SD 4.88)	14.90 (SD 5.19)	t (927) = 1.58 P = 0.115
After completion of three-year course	8.60 (SD 3.92)	14.73 (SD 4.42)	t (927) = 21.07 P = 0.000
Paired t- test	t (646) = 35.68 P = 0.000	t (281) = 1.12 P = 0.264	

[Table/Fig-3]: Type of therapy and change in mean symptom scores

Numerical Data				
	Group A		Group B	
Time of review	Mean symptom scores	Mean medication scores	Mean symptom scores	Mean medication scores
Beginning of the study	15.46	3.10	14.90	3.04
6 month	15.41	3.07	14.87	3.01
12 month	15.38	2.95	14.83	2.98
24 month	14.55	2.75	14.79	2.97
36 month	8.60	1.6	14.73	2.94



[Table/Fig-4]: Symptom and medication scores of the two groups during the three-year study period

There was no significant difference between the mean symptom scores of the two groups before intervention [15.46 (SD 4.88) v 14.90 (SD 5.19), P = 0.09] [Table/Fig-3]. However mean symptom score dropped sharply at the end of the study period in Group A in comparison to Group B [Table/Fig-4]. Statistically significant difference was observed between the mean symptom scores of the two groups at the end of the study period [8.60 (SD 3.92) v 14.73 (SD 4.42), P <0.001) [Table/Fig-3]. In both groups the mean symptom score decreased at the end of three-year course from the baseline (before intervention) but it differed significantly in Group A only [15.46 (SD 4.88) v 8.60 (SD 3.92), P<0.001] [Table/Fig-3]. The mean medication scores between the two groups also differed significantly at the end of the third year [1.60 (SD 0.31) v 2.98 (SD 0.44), P<0.001)]. The scores also decreased in both the groups from the baseline, but the difference was significant only in Group A [3.10 (SD 0.50) v 1.60 (SD 0.31), P<0.001] [Table/Fig-5].

Period of review	Mean medication score and standard deviation		Unpaired t- test
	Group A (n = 647)	Group B (n = 282)	
Before intervention	3.10 (SD 0.50)	3.04 (SD 0.64)	t (927) = 1.54 P = 0.124
After completion of three-year course	1.60 (SD 0.31)	2.98 (SD 0.44)	t (927) = 54.56 P = 0.000
Paired t- test	t (646) = 63.93 P = 0.000	t (281) = 1.74 P = 0.083	

[Table/Fig-5]: Type of therapy and change in mean medication scores

Around 8.0% (56/703) and 9.9% (31/313) of the study subjects were lost to follow-up from Group A and Group B respectively, but the difference was not found to be statistically significant (z = 0.82 P = 0.410).

No serious adverse events occurred in those who received SLIT (Group A). Around 6.4% (45/703) patients in this group complained of mouth and throat irritation and about 3.7% (26/703) complained of mild vomiting during the induction phase.

DISCUSSION

In order to improve the strength of evidence, the present study was carried out following a pre-post intervention design and keeping a comparison group at the same time. Tripathi DM et al (2008) conducted a study on efficacy of SLIT with multiple allergens following a quasi-experimental design where symptoms before and after the therapy, peak expiratory flow rate (PEFR), side effects and medications were studied. However no comparison group was kept in this study [16]. In the present study in order to assess the full effect of SLIT, the final evaluation was done by comparing the results obtained at the end of three years with that found before intervention at the beginning of the study both within and between the two groups.

It was seen in the present study that the common allergens were house dust, pollen, food, mites and fungi. Commonest pollens were Cynodon Dactylon, Cocos Nucifera, Peltophorum Pterocarpum, and Azadirachta Indica.

Tripathi DM et al (2008) in their study in Mumbai, India, on efficacy of SLIT with multiple allergens found that the most common allergens responsible for allergic asthma were house dust, house dust mites, pollen and fungi [16]. Commonest pollens were Amaranthus spinosus, Cocos nucifera, Peltophorum pterocarpum, Prosopis juliflora and Ricinus communis [16].

In the present study, the mean symptom score did not vary significantly in the two groups before intervention but the score was found to be significantly lower in Group A than in Group B at the end of the three-year course. It was also observed that the score decreased significantly from the baseline mean score in Group A only at the completion of the study. Similarly, the baseline mean medication score did not differ significantly from each other in the two groups. But it was significantly much lower in Group A than in Group B at the end of three years. Although the mean medication scores decreased in both the groups from the baseline, but that difference was significant only in Group A.

Results obtained from the study by Tripathi DM et al showed that there was significant reduction in symptom and medication scores at the end of three years in patients receiving SLIT with multiple allergens [16]. Marogna et al (2009) in an open randomized controlled trial (RCT) found that in patients with birch pollen–induced moderate asthma and rhinitis, the addition of SLIT provides a greater clinical benefit than that of Montelukast [3]. The upper and lower airway scores improved significantly in the SLIT group at years three and five compared to baseline [3]. Bronchial hyper-responsiveness and bronchodilator use decreased significantly in both groups at five years, but only in the SLIT group at three years [3]. Almost the same results were seen with a similar study on efficacy of SLIT in asthma due to grass pollen [17]. Another open RCT by D'Ambrosio et al (1996) in Parietaria allergic patients (aged 18 to 56 years) showed significant reduction in symptom score (P = 0.032) and drug plus symptom score (P = 0.037) as early as six months after starting sublingual immunotherapy [18].

In a meta-analysis on the efficacy of SLIT in asthma including 25 studies with an overall number of 1706 patients it was found that calculating the standardized mean difference (SMD), the reduction of asthmatic symptoms did not reach the statistical significance, but using the intention-to-treat method for outcome measures, significant decreases of asthma symptoms and drug consumption and significant improvements of lung function and bronchial hyperreactivity were detected [19].

A further meta-analysis examining nine studies dealing with mite-induced asthma found a reduction of symptoms (SMD = 0.95, *P* = 0.02) in 243 patients (adults and children) receiving SLIT compared to 209 receiving placebo. A reduction in rescue medication use was also found (SMD = 1.48, *P* = 0.02) [20].

In the present study, there was no report of serious adverse events in those who received SLIT (Group A). Around 6.4% patients in this group complained of mouth and throat irritation and about 3.7% complained of mild vomiting during the induction phase.

Bosquet et al (2009) reported that oro-pharyngeal reactions were the most common adverse events but other reactions, such as asthma, urticaria and abdominal pain had been reported with SLIT [21].

Lombardi in a study with mono-allergen (cat epithelia) in perennial allergic rhinitis and or bronchial asthma observed adverse effects in 7.5% with ultra rush sublingual swallow therapy. There were seven episodes of rhinitis, three of oral itching and one of abdominal pain [22]. There was no significant difference in adverse events in a study of 159 adult patients with allergic rhinitis and asthma (aged 16 to 59 years), who were treated with either a single allergen or multiple allergens [23].

Strengths and Limitations of the Study

The strength of this quasi-experimental study lies in having a comparison group and pre-test values for both the groups which helped in better evaluation of the efficacy of SLIT. The patients who received SLIT for three years are currently being followed up to assess the preventive efficacy. However, the major limitation of the study was non-randomization that might have lead to selection bias. There was no scope of blinding which might have brought forth some kind of subjective bias while reporting symptoms. Lost to follow-up could not be avoided although it was not significantly different in the two groups.

Implications for Future Research, Policy and Practice

The present study was to some extent demonstrated the efficacy and safety of SLIT with multiple allergens and is one of the few reports in this regard from the Indian subcontinent. The results from this study calls for conduction of randomized double blinded placebo controlled trials in this part of the world, considering the variety of allergens and the huge problem of environmental pollution. With further evidences, SLIT can play a major role in optimal management of asthma, particularly at primary care level.

CONCLUSIONS

It can be concluded from the present study that long term sub-lingual immunotherapy with multiple-allergens, in addition to rescue medicines significantly improves both symptom and medication scores with minimal side effects in allergic bronchial asthma. Unlike the conventional approach for management of bronchial asthma that aims at alleviation of symptoms, the main target of SLIT is focused on the aetiology and immuno-modulation. In the present study, the significant reduction in medication scores at the end of three years has implication towards possible cost-effectiveness of this approach by reducing the cost of using rescue medicines. However future studies are required to assess the long-term efficacy (preventive aspect) of SLIT. The subjects in the present study who received SLIT are currently being followed up for studying the disease free period. The sub-lingual route is supposed to hold a better prospect with regard to patient adherence to therapy than the sub-cutaneous immunotherapy (SCIT) which usually generates apprehension due to pain associated with injections. In general, SLIT appears to be associated with fewer and less severe adverse events than SCIT [21]. Considering the safety, ease of administration, convenience and clinical as well as cost effectiveness of this form of immunotherapy, operational researches are needed to be conducted to assess the feasibility of training and involving primary care physicians in SLIT for bronchial asthma.

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