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RESEARCH ARTICLE

SAFETY, TOLERABILITY AND CLINICAL EFFICACY OF ALLERGEN SPECIFIC CLUSTER SUBCUTANEOUS IMMUNOTHERAPY AMONG PATIENTS SUFFERING FROM NASO BRONCHIAL ALLERGY

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ABSTRACT

Background: Cluster subcutaneous immunotherapy can be identified to have the ideal schedule that allows the dose considered effective to be reached in the shortest possible time with the fewest adverse effects. There are very few studies on Cluster subcutaneous immunotherapy in India.

Methodology: The present study was conducted in Allergy clinic, KIMS Hospital & Research Centre, Bangalore for 18 months period. 40 Naso bronchial allergy patients in the 18–60 years age group who were positive for aeroallergens in skin prick test were recruited for cluster subcutaneous immunotherapy and followed for 12 months with symptom and treatment diary.

Results: Out of 40 patients, the majority, 30 (75.00%) patients were sensitive to house dust mites. All patients tolerated cluster SCIT none of them had any adverse reaction and there was significant decrease in both symptom-score and treatment score in these patients.

Conclusion: Cluster SCIT regimen has excellent safety, tolerability and clinical efficacy among Naso bronchial allergy patients.

INTRODUCTION

Allergen immunotherapy has been used for almost a century as a desensitizing therapy for allergic diseases. It also has the capacity for long term clinical effects and plays a protective role against the development of further allergies and symptoms.

The potential disease modifying effects of allergen specific immunotherapy are particularly compelling, considering their likely long duration of allergic symptoms, which require years of medications. In addition to the benefit of sustained remission of symptoms through allergen immunotherapy it also offers significant cost-benefit due to reduction in medication and other costs.

The traditional Conventional schedules for the initial phase of incremental doses have the disadvantage of the time needed to reach the maintenance dose with its attendant costs in terms of time and resources. Cluster schedules are designed to accelerate the buildup phase of immunotherapy leading to faster clinical improvement. Shorter regimens could simplify the administration and could be better accepted by patients, favoring their adherence to therapy

Controlled studies have shown symptomatic improvement and immunologic changes shortly after reaching maintenance doses by using cluster schedules.[1-5] A very few studies have evaluated the safety and efficacy parameters, still few have compared the efficacy of cluster schedule versus conventional schedules.[6-10]

In India there are a very few studies performed to identify the ideal schedule that allows the dose considered effective to be reached in the shortest possible time with the fewest adverse effects. Nevertheless, additional and larger studies with other types of allergens are needed to further confirm the safety and efficacy of such regimens. Hence, the present clinical trial was undertaken to study the safety, tolerability and clinical efficacy of Cluster subcutaneous immunotherapy among patients suffering from Naso bronchial Allergy.

Objectives

1. To describe the socio demographic profile of patients suffering from Naso bronchial allergy
2. To determine allergen sensitivity among Naso bronchial allergy patients.
3. To assess the safety and tolerability of Cluster Subcutaneous Immunotherapy based on adverse reactions.

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4. To assess the clinical efficacy of Cluster Subcutaneous Immunotherapy using symptom and treatment diary.

METHODOLOGY

Place of the study: The study was conducted in Allergy Clinic, Preventive Medicine Unit, Kempegowda Institute of Medical Sciences Hospital and Research Centre (KIMSH&RC), Bangalore.

Study period: 18 months.

Study design: Non – Randomized Non - Comparative clinical trial.
Sample size - 40 patients

Calculation of sample size

$\mathbf{n = 4pq/d^2}$

p – Prevalence [11] = 11%

q = 1 – p

With precision of 10%

$n = 4 \times 0.11 \times 0.89 / (0.10)^2 = 39.16$

Approximately 40 patients

Sampling method: Purposive sampling

Ethical issues and ethical committee clearance: The study was approved by the Institutional Ethics Committee (IEC) of KIMS and also registered in the Clinical Trials Registry of India, (CTRI) - **No: 2014/03/004487**

Source of data: Allergic rhinitis and allergic bronchial asthma patients who are sensitive to aero allergens with sensitivity levels of grade 2 and above.

Inclusion criteria: Patients between age group 18 – 60 years who have Allergic Rhinitis and Allergic

Bronchial Asthma and who are sensitive to aeroallergens.

Exclusion criteria

1. Patients not willing to take part in the study.
2. Patients with Severe Asthma, Pregnancy, Ischemic Heart Disease, High Blood Pressure, receiving Immunosuppressive medications & Beta-Blockers, and other Immune Disorders.

Collection of data

Individuals attending the Allergy Clinic of Kempegowda Institute of Medical Sciences Hospital and Research Centre with clinical signs and symptoms of Naso bronchial Allergy were subjected for a thorough history taking and routine investigations of Hb, TC, DC, ESR and Absolute Eosinophil count. Special investigations of Modified Allergy Skin testing were performed with 123 allergen extracts. The extracts included 19 pollens, 5 dusts, 2 dust mites, 10 fungi, 10 insects, 3 epithelia and 74 food allergens. Allergen extracts for skin prick tests were obtained from Creative Drug Industries, Navi Mumbai.

Individuals who are sensitive for aero allergens with sensitivity levels of grade 2 and above were included in the study and recruited for Cluster Subcutaneous Immunotherapy. Pollen antigens were selected based on pollen calendar. Premedication was given in an attempt to reduce the risk and severity of a systemic reaction two days prior to the procedure and 2 hours before the procedure. Informed written consent was obtained from the patient after informing about the nature and objectives of the study and then was subjected for

Cluster Subcutaneous Immunotherapy with the following schedule, as shown in Table 1. On the first visit, after recording the pulse rate and blood pressure, three injections of 0.2ml, 0.4ml and0.6ml was given subcutaneously with half an hour interval between each injection and recording the blood pressure and pulse rate at each interval and also noting down any adverse events during the procedure. This protocol is followed for each visit. This is the buildup phase of Cluster Subcutaneous Immunotherapy.

After the buildup phase is completed, i.e. after reaching the tolerable dose, the patient was continued on the maintenance dose of the immunotherapy medication for once in fifteen days for rest of the duration of the treatment. Patients were advised to report any adverse reactions which occurred during the maintenance phase. Subsequently, these patients were followed up for a period of 12 months to assess the clinical efficacy of the cluster subcutaneous immunotherapy.

Patients were given symptom diary and treatment diary and were instructed to enter the nature and frequency of symptoms and the rescue medications taken during the study period. Patient symptoms and treatment medications were coded and the patients were asked to enter on a daily basis. The treatment medications used were antihistamines 10 mg Cetirizine, 180 mg Fexofenadine & 25 mg Hydroxyzine and Mometasone & Loteprenol nasal sprays.

Statistical analysis

Descriptive statistics such as mean, standard deviation, frequency and percentage were used to describe nominal and ordinal data such as socio-demographic profile, allergen profile and adverse events.

RESULTS

Socio-demographic profile of Naso bronchial allergy patients

Out of 40 patients who were included in the study, majority i.e. 14 (35%) patients were in the age group of 35 – 44 years, followed by 11 (27.5%) in the age group of 25 – 34 years, 10 (25.0%) in the age group of 18 – 24 years & only 5(12.5%) patient were in the age group above 45 years. 26(65.0%) patients were females and the remaining 14(35.0%) were males. The age of the youngest and the oldest patient was 18 years and 60 years respectively. The mean age of the patients was 33.80 ± 10.89 years. The mean age of male and female patients was 37.50 ± 12.48 years and 31.81 ± 9.61 years respectively (Table 2). **(Figures in parenthesis indicates percentages)**

Table 1 Cluster Subcutaneous Immunotherapy Schedule

visit (week)	vial	volume	intervals
		0.2 ml	0 min
	Vial # 1 (1:25000)		
1		0.4 ml	30 min
		0.6 ml	60 min
		0.2 ml	0 min
	Vial#2 (1:2500)		
2		0.4 ml	30 min
		0.6 ml	60 min
		0.1ml	0 min
	Vial#3 (1:250)		
3		0.2ml	30 min
		0.3ml	60 min
		0.4ml	0 min
	Vial#3 (1:250)		
4		0.5ml	30 min
		0.6ml	60 min
		0.1ml	0 min
	Vial#4 (1:50)		
5		0.2ml	30 min
		0.3ml	60 min
		0.4ml	0 min
	Vial#4 (1:50)		
6		0.5ml	30 min
		0.6ml	60 min

Table 2 Distribution of Naso Bronchial Allergy patients according to their age and sex

Age group (years)	Male	Female	Total
18 – 24	02	08	10(25.0)
25 – 34	04	07	11 (27.5)
35 – 44	05	09	**14 (35.0)**
45 – 60	03	02	05 (12.5)
Total	14(35.0)	26(65.0)	40 (100.0)

Profile of Naso bronchial allergy patients according to their history and clinical examination

Out of 40 Naso bronchial allergy patients, majority i.e. 22 (55%) were suffering from Mild persistent Allergic rhinitis (According to ARIA guidelines) and 9 (56.25%) were suffering from Intermittent Bronchial Asthma (According to GINA guidelines) for a duration of 1---10 years. The mean disease duration was 6.65 ± 5.47 years [range 0.5---30 years] (Table 3).

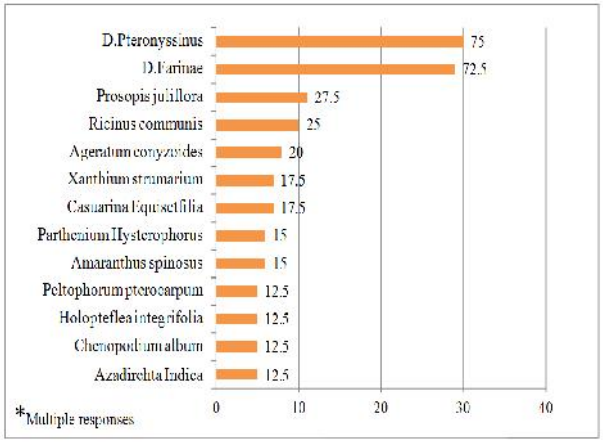
Table3 Distribution of Naso Bronchial Allergy Patients according to their duration of symptoms

Duration of symptoms	No. of Patients	Percentage
4 wks – 1 year	3	7.5
1 year – 5 years	16	**40.0**
5 years – 10 years	14	35.0
> 10 years	7	17.5
Total	40	100.0

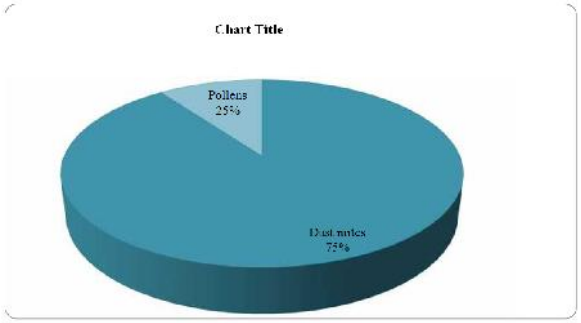
Out of 40 patients, 25 (62.5%) patients had a history of aggravation of symptoms in the early morning; 29 (80.6%) patients had a history of aggravation of symptoms on exposure to dust.20 (50.0%) patients had family history of atopy. Among them, 8 (40%) patients had family history of atopy in their maternal side and 11(55%) had family history of atopy in their paternal side, and 3(15%) patients had family history of atopy in their siblings.

Profile of allergen positivity among Naso bronchial allergy patients

Among 40 patients recruited for cluster subcutaneous immunotherapy, majority i.e. 30 (75%) were given immunotherapy for house dust mites (Dermatophagoides farinae and Dermatophagoides pteronyssinus) and the remaining 10 (25%) patients were given immunotherapy for one or more pollens such as grass pollens (Cynodon dactylon, Sorghum vulgare and Typha angustata), Tree pollens (Prosopis juliflora, Peltophorum Pterocarpum, Cassia siamea, Ailanthus excelsa, Acacia arabica, Casuarina equisetfolia and Holopteflea Integrifolia) and Weed pollens (Dodonea viscose, Ageratum conyzoides, Xanthium Strumarium, Parthenium hysterophorus, Amaranthus spinosus and Chenopodium album) (Graph. 1&2).



Graph 1 Distribution of Naso Bronchial Allergy patients according to their Allergen sensitivity (n=40)



Graph 2 Distribution of Naso Bronchial Allergy patients according to their Allergen specific immunotherapy profile (n=40)

Tolerability and Safety of Cluster Subcutaneous immunotherapy

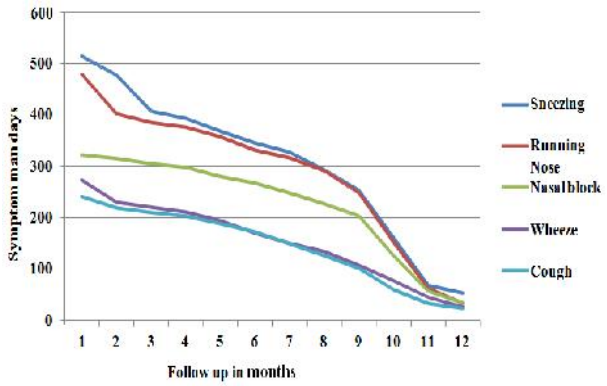
Out of 40 patients, 22 (55 %) tolerated 1:50 concentration dosage at 6 weeks and reached the maintenance dose,22 (55.5%) tolerated 1:250 concentration dosage at 4 weeks and 35 (87.5%) patients tolerated 1:2500 concentration dosage at 2 weeks duration and subsequently reached maintenance dose. The mild local reactions (Redness, Pruritus and Induration) subsided on its own without any medications. There was no any systemic reaction (Table 4).

Assessment of clinical efficacy of Cluster Subcutaneous immunotherapy

The patients were given a symptom diary and treatment diary, instructed to enter the nature and frequency of symptoms and rescue medications taken, and followed up for 12 months to assess the clinical efficacy of Cluster Subcutaneous immunotherapy. It was observed that the number of symptom

man-days (number of days the patient had symptoms) decreased gradually over a period of 12 months follow up showing good clinical efficacy which was statistically significant (Graph. 3).

Similarly, the number of treatment man-days (number of days on which the patient was on rescue medications) decreased gradually over a period of 12 months follow up, showing good clinical efficacy which was statistically significant [Friedman test, *Fr* = 230.924, *P* = 0.001] (Graph. 4).



Graph 3 Line diagram showing symptom man- days among cluster SCIT patients

some protocols. This schedule can permit a patient to reach a maintenance dose in as brief a period of time as 4 weeks. The cluster schedule is associated with the same frequency of systemic reactions compared with immunotherapy administered with conventional schedules. The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of premedication two days prior to and 2 hours before dosing.[12]

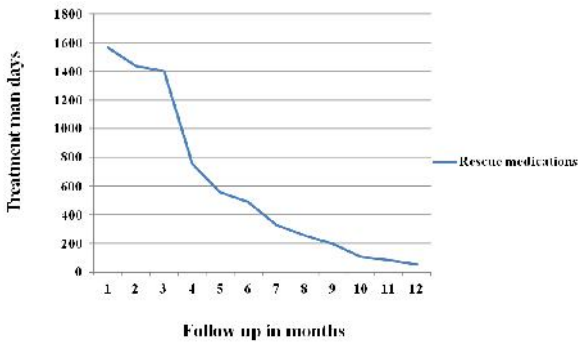
In the present study, the mean age of the patients was 33.80 ± 10.89 years (range 18---60 years). The mean age of male and female patients was 37.50 ± 12.48 years and 31.81 ± 9.61 years respectively. This observation differs from the study conducted by Serrano.P *et al* were the mean age of the patients was 25 years (range 16 – 50years)[5]. In Tabar *et al* study[1], among 239 patients, 120 patients were in the cluster group and 119 patients were in the conventional group. Among 120 patients there were 75 male participants and 45 female participants (mean age 19.34 ± 9.8 years). Among 119 patients there were 71 male participants and 48 female participants (mean age 18.47 ± 9.49 years).

The mean disease duration was 6.65 ± 5.47 years. This was longer than in the study conducted by Tabar *et al*[1], where the mean disease duration was 4.84 years. In the present study Family history of Atopy was present in 20 (50.0%) patients.

Table 4 Safety and Tolerability of Cluster Subcutaneous Immunotherapy

Concentration	No. of Patients Tolerated	Duration	Local Reaction(LR)	Systemic Reaction (SR)	Remarks
1:25000	**40(100.0)**	1 week	Nil	Nil	All tolerated.
1:2500	35(87.5)	2 weeks	Mild*	Nil	Cluster stopped for 5 patients due to LR's but treatment continued.
1:250	22(55.0)	4 weeks	Mild*	Nil	Cluster stopped for 13 patients due to LR's but treatment continued.
1:50	22(55.0)	6 weeks	Nil	Nil	22 patients reached maintenance dose in 6 weeks.

*Mild (Redness, Pruritus and Induration)



Graph 4 Line diagram showing treatment man-days among Cluster SCIT patients

DISCUSSION

Cluster schedules are designed to accelerate the buildup phase of immunotherapy. It is usually characterized by visits for administration of allergen immunotherapy extract 1 or 2 times per week with a schedule that contains fewer total injections than are used with conventional immunotherapy. With cluster immunotherapy 2 or more injections are given per visit on nonconsecutive days. The injections are typically given at 30-minute intervals, but longer intervals have also been used in

According to ARIA guidelines, majority i.e. 22 (55%) were suffering from Mild persistent Allergic rhinitis 10 (25%) were suffering from Mild Intermittent Allergic rhinitis and 4(10%) each were suffering from Moderate – severe Intermittent Allergic rhinitis and moderate to severe persistent Allergic rhinitis, According to GINA guidelines, 9 (56.25%) were suffering from Intermittent Bronchial Asthma and the remaining 7 (43.75%) were suffering from Mild persistent Bronchial Asthma in the present study.

Tabar *et al*[1] studied 239 patients with a history of mild - moderate rhinitis or bronchial asthma. Whereas Serrano. P *et al*[5] studied on 61 mild to moderate asthma patients and 30 rhino conjunctivitis patients. Zhang. L *et al*[4] in their study observed 96 allergic rhinitis patients.

In the present study, the patients were sensitive to house dust mites (Dermatophagoides farinae and Dermatophagoides pteronyssinus) and pollens such as grass pollens (Cynodon dactylon, Sorghum vulgare and Typha angustata), Tree pollens (Prosopis juliflora, Peltophorum Pterocarpum, Cassia siamea, Ailanthus excelsa, Acacia arabica, Casuarina equisetfolia and Holopteflea integrifolia) and Weed pollens (Dodonea viscose, Ageratum conyzoides, Xanthium Strumarium, Parthenium

hysterophorus, Amaranthus spinosus and Chenopodium album).

Whereas in the study conducted by Tabar *et al*[1] and Zhang. L *et al*[4] patients who were sensitive to House dust mites were included. In Nanda. A *et al*[2] study, patients who were sensitive to cat dander, were included.

In the present study, all the patients tolerated the complete dosage of Cluster SCIT regimen. No patient discontinued the treatment due to adverse events, and no serious adverse events or life threatening anaphylactic reactions were reported which was similar to Serrano. P *et al* study[5] where all patients tolerated the treatment very well. The results of Zhang.L *et al* study[4] demonstrated similar SR rates of cluster schedule as compared to conventional schedule. Whereas the findings from Tabar *et al* study[1] where there were no differences between the 2 schedules in frequency or type of adverse events.

In the present study, it was observed that both the number of symptom man days (number of days the patient had symptoms) and also the number of treatment man days (number of days on which the patient was on rescue medications) decreased gradually over a period of 12 months follow up ($p=0.001$). Which was similar to the study conducted by Tabar *et al*[1] where there was a marked and significant ($p < 0.03$) decrease of the symptom score (about 52%) and medication score (about45%) in the active treatment group.

CONCLUSION AND RECOMMENDATIONS

The limitation of this study is that Long term benefits of cluster subcutaneous immunotherapy in the heterogeneous study subjects could not be studied because of time constraints. Although a randomized control study would be the appropriate study design, it was not done due to feasibility and ethical constraints. To conclude, cluster subcutaneous immunotherapy regimen has excellent safety, tolerability and clinical efficacy among patients suffering from Naso bronchial allergy.

Hence cluster subcutaneous immunotherapy can be recommended as an alternative to conventional subcutaneous immunotherapy. There is a need for further studies like randomized controlled trials involving a larger sample size and with a longer follow-up period

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