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AN OPEN LABEL PILOT STUDY TESTING THE ROLE OF CLASSICAL HOMEOPATHY IN CHRONIC ALLERGIC RHINITIS

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ABSTRACT: Purpose: The prevalence of allergic rhinitis (AR) is increasing at an alarming rate throughout the world. India has an estimated number of 15-20 million patients with allergic bronchial asthma and 30-80% of these suffer from AR. So, AR is considered as a major chronic respiratory disease due to its prevalence, impact on quality of life (QoL), work/school performance and productivity, economic burden and links with asthma. This research aims at testing the role of classical homeopathy in bringing changes in serum immunoglobulin E (IgE) level and absolute eosinophil count (primary outcome measures) and symptoms score and WHOQOL-BREF score related to AR (secondary outcome measures) by comparing the pre-trial and post-trial data.

Method: An open label, single arm, experimental, prospective, non-randomized, non-controlled, before and after comparison pilot study was carried on 34 participants suffering from chronic AR. Institutional ethical clearance was obtained; then thirty four consenting patients were enrolled after screening of 58 patients by eligibility criteria and were allocated to classical homeopathic treatment. Four cases were drop-outs; thirty cases were regular. Outcome measures were assessed and analyzed after one year.

Results: After one year of homeopathic treatment, lowering of serum IgE level (1006.83±395.17 *vs* 336.5±126.96; P = 0.0000), absolute eosinophil count of blood (600.33±103.61 *vs* 302.5±82.21; P = 0.0000) and AR symptoms score (30.27±5.12 *vs* 12.83±2.72; P = 0.0000) and increase in WHOQOL-BREF scores of AR (58±7.01 *vs* 87.7±6.18; P = 0.0000) were statistically highly significant. No adverse effects and/or complications were observed. Most commonly used constitutional and acute remedies were *Natrum muriaticum* and *Histamine hydrochloride* respectively in different centesimal potencies.

Conclusion: Data suggest that classical homeopathic treatment may be a useful measure for the patients suffering from chronic AR. However, multi-centric randomized controlled trials with larger sample size should be undertaken for making firm recommendations.

INTRODUCTION: AR is a disorder of upper airways resulting from IgE mediated inflammation upon contact of nasal mucosa with allergens and is characterized by rhinorrhea, nasal pruritus, sneezing, congestion and nasal obstruction, occasionally associated with conjunctival symptoms [1-4], while two or more symptoms occurring for more than one hour on most of the days [5, 6]. AR may be intermittent with symptoms occurring on less than 4 days out of 7 or for less than 4 weeks per year or persistent with symptoms occurring on at least 4 days out of 7 or for more than 4 weeks per year [5, 7].

Nasal biopsy in AR reveals accumulation of mast cells, eosinophils and basophils in epithelium and eosinophils in deeper sub-epithelium, i.e. lamina propia [7]. Allergic Rhinitis (AR) and Bronchial Asthma (BA) are symptomatically as well as pathophysiologically overlapping and frequently co-existing morbid conditions [8 – 12] with AR being a major risk factor for occurrence of asthma [2, 13]. The two together can be referred to as "chronic allergic respiratory syndrome" [2, 14, 15] or "chronic allergic total airways disease syndrome" [1, 16, 17].

According to the estimates of WHO, approximately 150 million people worldwide are affected by asthma and more than 1, 80,000 deaths are due to asthma each year. India has an estimated number of 15-20 million patients with asthma and 30-80% of these suffer from allergic rhinitis [1, 18]. So, allergic rhinitis is considered as a major chronic respiratory disease due to its prevalence, impact on quality of life, work/school performance and productivity, economic burden and links with asthma [19]. Despite significant progress in the pathophysiology of AR and BA and availability of several therapies in recent years, a true and complete cure for these two so far seems out of reach [1].

As per recurrence, AR may be classified into intermittent (IAR; symptoms <4 days/week or < 4 consecutive weeks) and persistent (symptoms >4 days/week and >4 consecutive weeks) varieties. Again, according to severity, AR may be mild (normal sleep, no impairment of daily activities, sports, leisure, no impairment of work or school, symptoms present but not troublesome) or moderate to severe (sleep disturbance, impairment of daily activities, sports, leisure, impairment of school or work and troublesome symptoms) [20].

Pharmacological therapy chiefly focuses on Leukotriene receptor antagonists (Montelukast, Pranlukast etc.), oral/intranasal 2nd generation antihistamines, intranasal steroids and anti-IgE antibodies (e.g. Omalizumab) [20-23]. However, strict avoidance of offending allergens is considered to be the safest and most effective treatment of all available therapies [24].

Sub-lingual, nasal or subcutaneous immunotherapy is the only therapeutic option that modifies the basic allergic mechanism by inducing desensitization and producing an anergy state for offending allergens (e.g pollen, house dust mite etc.) [25-28].

Most of the clinical trials conducted in homeopathy on AR till date chiefly focussed on testing isopathy, immunotherapy, same drug or formula in all patients, clinico-pathogenetic trials [29-44] and only a few tried classical 'individualized' approach [46, 47]. But also in these classical homeopathic trials subjective outcome parameters (symptoms score) were used; no reproducible, objective, validated, pathological/ biochemical outcome measures were used. In that sense, this pilot study is a pioneer work in the field of evidence-based homeopathic research.

Primary objective of this trial was to evaluate the role of homeopathic medicines in the management of AR using two validated primary outcome measures (serum IgE level and absolute eosinophil count) and secondary objective was to ascertain the efficacy of homeopathic remedies in AR by using another two validated secondary outcome measures (symptoms scoring and total WHOQOL-BREF scoring for AR). (**Table 1**; see later)

MATERIAL & METHODS:

Clinical Trials Registry of India Number: "CTRI/2012/12/003193" (Date – Dec 7, 2012)

Universal Trial Number: "U1111-1136-4297" (Date – Oct 27, 2012)

Protocol Identification Number: "102/MBHMCH/CH/ADM/10" (Date – Oct 25, 2010).

A single arm, experimental, prospective, non-randomized, non-controlled, short-term, before and after comparison pilot trial was carried out on 30 patients suffering from AR at Mahesh Bhattacharyya

Homeopathic Medical College & Hospital, Government of West Bengal, Drainage Canal Road, Doomurjala, Howrah, West Bengal, India from November, 2010 to December 2011. The study protocol was completely in accordance with the Helsinki declaration on human experimentation [48] and Good Clinical Practice (GCP) [49].

Clearance was obtained from the ethical committee of the institution. Consequently, before recruitment, each participant was explained verbally about the study with the help of Patient Information Sheet and thereafter a written consent was obtained from them. However, they were free to withdraw from the study at any point of time. Proper care was taken that this trial with 'intention to treat' did not cause any harm to any individual.

Samples were chosen from the out-patient department of the hospital and only those fulfilling the eligibility criteria were recruited in the trial after obtaining their written informed consent.

Inclusion criteria included diagnosed cases of AR of minimum 1 year duration, both intermittent (seasonal and perennial) and persistent varieties of AR, both mild and moderate to severe AR, age between 18 and 65 years, both sexes, atopic (reactive to allergens with positive skin prick test results) and/or eosinophilia, cases with controlled (intermittent and mild) bronchial asthma without regular medication, and written informed consent from the patient.

Exclusion criteria consisted of gross nasal developmental defects or structural abnormalities causing obstruction, e.g. nasal polyp(s), deviated septum etc., previous homeopathic immunotherapy for allergic rhinitis, allergen avoidance in past 6 weeks, avoidance of usual environment for more than 1 week during trial, severe asthma cases as detected clinically, respiratory infection, cases with induced severe/uncontrolled bronchial asthma, presence of severe concomitant or any systemic disease(s) like cardiovascular, endocrinal, renal etc., pregnancy, breast feeding, or likelihood of pregnancy, oral or parenteral steroids and/or decongestant in past 6 months, conventional desensitization in past 6 months, and if any of these mentioned exclusion criteria would have developed during the trial, case would be excluded.

The study was of one year and two months duration. Patient recruitment was continued for first two months and follow-up for one year. Before recruitment in the trial, all the consenting participants were subjected to preliminary screening looking for presence of signs and symptoms and/or diagnosed cases of AR, thereby qualifying for the eligibility criteria mentioned.

Then the qualified (preliminary screening) subjects were undergone detailed screening by assessing for baseline data using two primary outcome measures, i.e. serum immunoglobulin E level and absolute eosinophil count and two secondary outcome measures, i.e. the symptoms scoring and total WHOQOL-BREF scoring for AR.

The primary outcome measures were already validated. Serum total IgE by ELISA (usual range in AR: 450-800 IU/ml) [50, 51] was considered to be a sensitive and reliable biomarker of AR, because it was less invasive, not affected by drugs such as anti-histamines and could be adopted in patients with dermographism [52].

Eosinophils were one of the central effector cells and essential components of initiation and propagation of hypersensitivity reaction. Absolute eosinophil count in AR usually ranges from 283-800 cells/cmm with no significant diurnal variation [50, 51].

The symptom scoring scale for AR used in this trial was developed and previously used in a clinical trial on AR by the Central Council for Research in Homeopathy, Dept. of AYUSH, MoH&FW, Govt. of India [46] (Table I) with some modifications from other sources [53, 54].

This modified symptom scoring scale was validated independently by the institutional review board and also five external conventional medicine experts (two medicine experts, one pulmonologist, one ENT specialist and one allergologist) neutral about homeopathy. The WHOQOL-BREF scoring scale was developed by World Health Organization (WHO) [55]. Necessary permission was taken from WHO for use of the tool in this trial.

TABLE I: ALLERGIC RHINITIS SYMPTOMS SCORE

Symptoms/Signs	Scores				
	0	1	2	3	4
Running nose	Absent	Watery, thin	Mucoid, thick, white	Muco-purulent, yellowish green	--
Discharge (sensation)	Absent	Bland	Acrid	--	--
Discharge (quantity)	Absent	Scanty	Copious	--	--
Sneezing	Absent	Occasional	Infrequent	Constant	--
Nasal obstruction (frequency)	Absent	Occasional	Always	--	--
Nasal obstruction (side)	Absent	Uni-lateral	Bi-lateral, compelling to breathe through mouth	Post-nasal dripping	--
Irritation in nose and eyes	Absent	Itching	Burning	Pain	--
Irritation in throat	Absent	Itching	Burning	Pain	--
Lachrymation (quality)	Absent	Bland	Acrid	--	--
Lachrymation (quantity)	Absent	Occasional	Always	--	--
Malaise	Absent	--	--	Present	--
Congestion of nasal mucosa	Absent	--	--	Swollen, red	--
Congestion of nasal turbinates	Absent	--	--	Swollen, red	--
Fever	Absent	Mild (97-99°C)	Moderate (99-101°C)	Severe (101-105°C)	Hyperpyrexia (≥105°C)
Headache	Absent	Present	--	--	--
Anosmia	Absent	Present	--	--	--

Case taking was done as per the case recording format (CRF) developed as per the guidelines laid down by Hahnemann in Organon of Medicine [56] and Kent's philosophy [57] and individualized constitutional homeopathic medicines were prescribed in different centesimal potencies as judged applicable to the patients' status by the treating physicians. Medicines were selected on the basis of totality of symptoms, followed by repertorization by Kent, Boenninghausen, Boger-Boenninghausen and Synthesis repertories using RADAR© software. After repertorization, however, the portrait of the drug was confirmed by consultation with the Materia Medica [58, 59]. Thus the study was not deviated from the basic principle of homeopathy, i.e. individualization.

A single dose of constitutional medicine was prescribed to be taken orally in 30cH potency in each case initially, and depending on the intensity of the complaints, the medicine was repeated in required potencies. Each dose consisted of a single drop of the homeopathically selected medicine in 15 ml of distilled water and was dispensed in amber-colour glass vials. The medicines were procured from a GMP certified pharmaceutical SBL Pvt. Ltd. The patients reported in 24 hours, one week or so as per need. They were followed up clinically at one month interval and the scoring was done by the investigator. Indicated medicine was repeated depending on the intensity of the symptoms till perceptible change appeared (improvement of signs and symptoms). Appearance of any change was immediately followed by placebo or change in remedy, according to response. Repetition was done 2 to 6 hourly or even oftener, depends upon the intensity of symptoms, i.e. 6 hourly in mild cases, 4 hourly in moderate cases, and few minutes to 2 hours in severe cases. Medicine was repeated following Kent's 12 observations [57].

In case of acute exacerbation of chronic AR or any other acute disease/condition (e.g. fever, acute gastro-enteritis etc.) arising during the course of treatment, prescription were changed and selection of the medicine were based on the prevailing characteristic symptoms including exciting cause, mental and physical generals and qualified particular symptoms modified as a consequence of acute disease. The medicines selected were either continuation of the homeopathic constitutional medicine or a new remedy worked out for acute totality. Treatment of chronic disease after the acute exacerbation/acute disease had subsided was made depending on the state of signs/symptoms of the chronic disease i.e. the medicine in suitable potency was given or placebo was continued.

Cases were followed up as per approach towards chronic case. Patients received the previously assigned treatment or after the acute exacerbation/acute disease had subsided, the case was reassessed and if there was difference in the totality of the symptoms, another appropriate medicine was prescribed.

A follow up and observation of these subjects were done for one year. At the timeline of one year, the patients were reassessed on the same outcome measures. Efforts were made to ensure compliance of instructions and adherence to the prescribed therapeutic schedule.

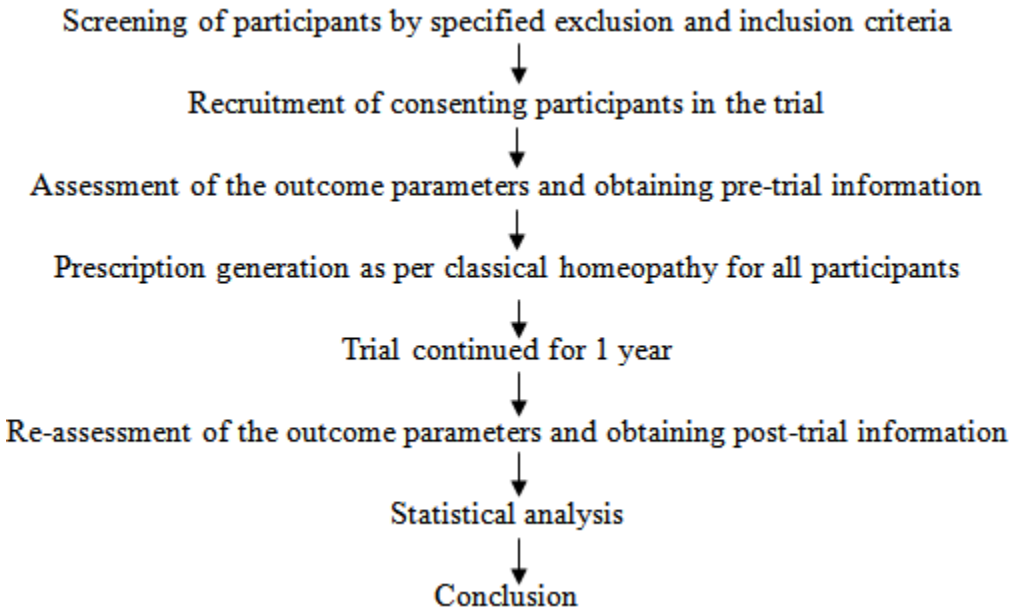
Primary study endpoints were statistically significant changes in the serum IgE level and absolute eosinophil count at 12 months. Secondary study endpoint was changes in the symptoms score and WHOQOL-BREF score at 12 months interval. Safety end-point was any (serious) adverse event or complication(s) arising during the trial. It was the responsibility of the investigators to maintain the patient in the study, provided it was safe to do so.

A patient might be discontinued from the study with proper documentation for either clinical failure (i.e. no change in symptomatology and/or aggravation of complaints) or occurrence of any (serious) adverse event (i.e. no improvement in symptoms score and WHOQOL-BREF score from baseline assessment score, any serious intercurrent illness, injuries or experience developing/worsening in severity during the course of the trial, any fatal or life-threatening events requiring /prolonging hospital stay, persistent or significant disability or incapacity or any important medical events). Data were extracted from the reports directly and independently. A consent form, patient information sheet, standard data record proforma, symptom scoring form, WHOQOL-BREF scoring form, repertorial analysis form, treatment form, compliance form and intercurrent acute illness and treatment record form were used by the investigators. All these were compiled at the end; data were extracted and analyzed. Missing data were retrieved by regular scrutiny of records and defaulter retrieval. All the source documents (evaluation forms, reports and records) were kept in strict confidentiality and would be retained for further five years.

The approach of statistical analysis was as per protocol. Pre-trial and post-trial data obtained were verified and analyzed using statistical paired *t* test. Only the protocol compliant patient population from the treated/enrolled population were subjected to statistical analysis in the end.

Centralized workshops were organized every 2 months for all the research team members to ensure standardization, accuracy, completeness and quality control. Treatment conditions and records were repeatedly verified by the institutional review board at frequent intervals of 3 months for quality assurance. A training module was developed detailing out various modes of training to be imparted to the concerned research workers.

The study flow diagram was as follows:



RESULTS: Out of the 58 screened patients, 34 were recruited; 30 patients completed the trial and 4 were drop-outs. These 30 patients were included in the final analysis.

Demographic data revealed that most of the patients were in the age group of 18-30 years (n=22; 64.71%). Others were in the age group of 31-40 years (n=8; 23.53%), 41-50 years (n=3; 8.82%) and 51-60 years (n=1; 2.94%). M±SD expression of the study sample was 29.26±9.45. Sex ratio was M: F = 15 (44.12%): 19 (55.88%). Habitat ratio was rural: urban = 12 (35.29%): 22 (64.71%). Economic class ratio was poor: affluent = 11 (32.36%): 23 (67.64%). Most of the patients were allergic to house dust (n=11; 32.35%), followed by smoke/fumes, weather change, cooking oil and pollen (each n=4; 11.76% each); damp (n=2; 5.88%); and smog, cockroach and cats (each n=1; 2.94% each). Positive family history was found in 26 patients (76.47%). Controlled (intermittent and mild) bronchial asthma without regular medication was present in all the 34 (100%) study subjects.

All of the analyzed patients (n=30; 100%) showed changes in favor of homeopathy both in terms of primary and secondary outcome measures.

After one year of homeopathic treatment, following changes in the primary and secondary outcome measures were observed: (**Table 2**)

1. Serum IgE level was lowered from 1006.83±395.17 to 336.5±126.96, which could be considered as statistically highly significant (t_{29} = 10.84; P = 0.0000)
2. Absolute eosinophil count of blood was lowered from 600.33±103.61 to 302.5±82.21, which was also statistically highly significant (t_{29} = 18.17; P = 0.0000)
3. The symptoms scores of AR showed lowering from 30.27±5.12 to 12.83±2.72, which was also statistically highly significant (t_{29} = 22.37; P = 0.0000).
4. The total WHOQOL-BREF score showed increase from 58±7.01 to 87.7±6.18 which was also statistically highly significant (t_{29} = 39.28; P = 0.0000). Individual domain scores showed following changes – (Table III, Chart I)
   a. Domain I (Physical): Score increased from 16.6±3.25 to 27.4±2.96 (t_{29} = 19.72; P = 0.0000)
   b. Domain II (Psychological): Score increased from 14.2±3.18 to 24.0±2.16 (t_{29} = 5.43; P = 0.0000)
   c. Domain III (Social): Score increased from 7.03±1.75 to 10.0±1.59 (t_{29} = 18.66; P = 0.0000)
   d. Domain IV (Environmental): Score increased from 16.4±3.67 to 18.4±3.94 (t_{29} = 11.58; P = 0.0000)

TABLE 2: COMPARISON BETWEEN PRE-TRIAL AND POST-TRIAL DATA

Outcome Measures	Before Intervention (M±SD)	1 year after intervention (M±SD)	*t* score at df=29	P value and significance
Serum IgE level (IU/ml)	1006.83±395.17	336.5±126.96	10.84	P = 0.0000; highly significant
Blood absolute eosinophil count (cells/cmm)	600.33±103.61	302.5±82.21	18.17	P = 0.0000; highly significant
Symptoms score of AR	30.27±5.12	12.83±2.72	22.37	P = 0.0000; highly significant
Total WHOQOL-BREF score	58±7.01	87.7±6.18	39.28	P = 0.0000; highly significant

TABLE 3: CHANGES IN INDIVIDUAL DOMAIN SCORES OF WHOQOL-BREF

Domains of WHOQOL-BREF	Before Intervention (M±SD)	1 year after intervention (M±SD)	*t* score at df=29	P value and significance
Domain I	16.6±3.25	27.4±2.96	19.72	P = 0.0000; highly significant
Domain II	14.2±3.18	24.0±2.16	5.43	P = 0.0000; highly significant
Domain III	7.03±1.75	10.0±1.59	18.66	P = 0.0000; highly significant
Domain IV	16.4±3.67	18.4±3.94	11.58	P = 0.0000; highly significant

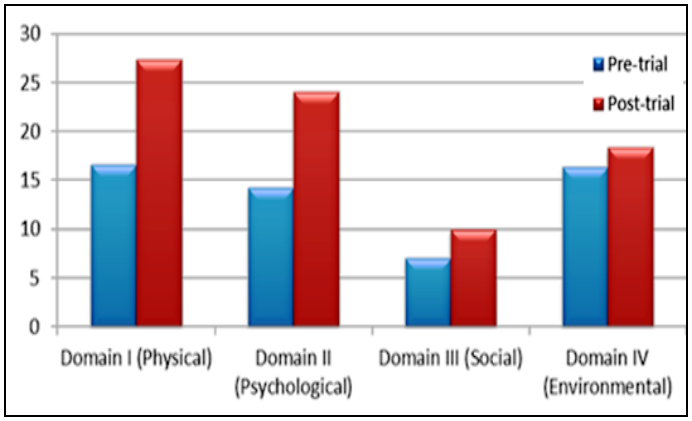


CHART 1: CHANGES IN DOMAIN SCORES OF WHOQOL-BREF

There was a total drop-out of 4 cases (11.76%) in the trial. One subject withdrew himself voluntarily from the study; one was referred to conventional medicine for sudden deterioration of condition after due consultation with the conventional medicine expert; one was excluded due to failure to follow-up for minimum required duration/investigations for the conduct of analysis, and one got injured and fractured clavicle during the course of study and attended other treatment (**Table 4**).

TABLE 4: ATTRITION RATE

Total number of patients (n)	Number of drop-outs (n) (%)	Reasons for drop-out
34	4 (11.76%)	a) Subject(s) withdrew themselves from the study (n=1) b) Referred to conventional medicine for sudden deterioration of condition after due consultation with the expert (n=1) c) Failed to continue follow-up for minimum required duration/investigations for the conduct of analysis (n=1) d) Fractured clavicle during the course of study and attended other treatment (n=1)

No adverse effects and/or complications were observed.

Constitutional remedies were prescribed to all 34 recruited patients. The most frequently prescribed constitutional homeopathic medicines were *Natrum muriaticum* (n=6), *Psorinum* (n=6), *Lachesis muta* (n=4), *Bacillinum* (n=3), *Nux vomica* (n=3), *Tuberculinum bovinum* (n=3), and *Sulphur* (n=3). *Natrum sulphuricum* and *Medorrhinum* each was used in single cases (**Table 5**). Different acute remedies (‘rescue medications’) were prescribed 149 times throughout the study. The homeopathic medicines which were most frequently prescribed on acute totality were *Histamine hydrochloride* (35 times), *Arsenicum iodatum* (19 times), *Allium cepa* (18 times), *Euphrasia officinalis* (16 times), *Arsenicum album* (16 times), *Sabadilla* (14 times), *Sanguinaria canadensis* (13 times), *Sanguinaria nitricum* (10 times) and *Aralia racemosa* (8times) (Table 5).

TABLE 5: USED REMEDIES

Medicines withpurpose of use	Name of the medicines	Prescriptions
Constitutional remedies	*Natrum muriaticum*	6 cases (17.65%)
	Psorinum	6 cases (17.65%)
	Lachesis muta	4 cases (11.76%)
	Bacillinum	3 cases (8.825%)
	Nux vomica	3 cases (8.825%)
	Sulphur	3 cases (8.825%)
	Tuberculinum bovinum	3 cases (8.825%)
	Medorrhinum	1 case (3.33%)
	Natrum sulphuricum	1 case (3.33%)
Acute remedies (‘rescue medications’)	*Histamine hydrochloride*	35 times (23.49%)
	Arsenicum iodatum	19 times (12.75%)
	Allium cepa	18 times (12.08%)
	Euphrasia officinalis	16 times (10.74%)
	Arsenicum album	16 times (10.74%)
	Sabadilla	14 times (12.07%)
	Aralea racemosa	13 times (8.72%)
	Sanguinaria Canadensis	10 times (6.71%)
	Sanguinaria nitricum	8 times (5.37%)

DISCUSSION: Smaller sample size was considered in this trial in comparison to other published trials on AR [9, 10]. Besides, due to limited resource and infrastructure, frequent repetition of pathological/biochemical tests were not possible. Also, though explained extensively to the participants, chances of 'threats to external validity' could not be completely avoided due to chances of interaction with other forms of therapy and interaction of testing and treatment (evidence that testing might be related to the treatment so that subjects complete tests differently after treatment). Attempts were made to minimize 'threats to construct validity' by minimizing chances of inadequate explication, mono-method bias, hypothesis guessing, evaluation apprehension, and experimenter bias [23].

However, classical homeopathy was tested in this study revealing a positive outcome on two reproducible, objective and validated outcome parameters (serum IgE and absolute eosinophil count) apart from two validated, but subjective outcome measures, i.e. symptoms scoring and WHOQOL-BREF scoring. Further, the objective of this study was to evaluate the role of classical homeopathy in AR rather than to evaluate or suggest any single or group of homeopathic remedy(ies). Larger trials in future may suggest a sub-group of remedies that are more frequently indicated in this clinical condition.

Homeopathic medicines were effective especially in cases with considerable number of characteristic symptoms. The final differentiation of the remedies were made after reference to different Materia Medica, and a remedy matching the totality was chosen, taking care that it also corresponded to the predominant miasmatic influence in the case. In some cases, especially where characteristic symptomatology and precise prescribing totality was lacking, remedy selection was influenced by constitutional attributes, generalities and the fundamental cause, i.e. the chronic miasm in background.

Treatment often was difficult due to this fundamental miasm; sometimes improvement ceased even after administration of a well-selected remedy; sometimes, remedies failed to make any impression in spite of certain indications; occasionally they completely obscured the symptomatology. These cases required intercurrent anti-miasmatic remedies to remove the block. Prescription in such an instance became presumptive rather than a certainty, and success or failure of the selected remedy was indicated only on serial assessment of outcome measures, in the absence of demonstrable aberration in health. During the follow up visits, the remedy was repeated only when necessary, in the same potency or with a change in potency as indicated. Likewise, a change in remedy also was considered only when essential, after careful evaluation of the follow up. In cases where both were not necessary, only placebo was prescribed.

Future research options in this field should aim at taking basophils, mast cells, eosinophilic cationic protein (ECP), eosinophil protein X, cytokines (IL-5), specific IgA, and various chemokines (e.g. stromal cell derived factor 1, RANTES, eotaxin, PGD2, leukotrienes etc.) of nasal mucosal lavage of AR patients as outcome measures [60-64].

CONCLUSION: The trial findings were encouraging and our data suggested that homeopathic treatment might have beneficial effects in patients suffering from chronic AR. However, in order to build credibility within the medical research field, multiple replicative research and/or extensions using the same or similar approaches to treat the same or similar medical conditions or in multi-centric, randomized, controlled design is required on larger sample size for improving the confidence level and testing the generalizability and applicability of the trial findings and making firm recommendations.

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