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A randomised, double blind, placebo-controlled, multi-centric parallel arm trial to assess the effects of homoeopathic medicines on chronic rhinosinusitis

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) is one of the most common illnesses interfering with patient's quality of life and work. Observational studies conducted by the Council indicate positive outcome. This protocol has been developed to ascertain the usefulness of homoeopathic intervention in comparison with control group in a randomised control setting.
Objectives: Primary objective is to evaluate the changes in TSS (Total Symptoms Score) and SNOT-22 (Sino-nasal Outcome Test-22) within the two groups of the study (Homoeopathy + Placebo). Secondary objective is to evaluate changes in SNOT-22 at end of the trial, changes in Lund and Mackay staging of CT scan, rhinoscopy grading, absolute eosinophil count, global assessment by investigator and patient, and number of acute exacerbations of CRS (for frequency, duration and intensity) as per TSS scale compared to placebo.
Methods/Design: This is a randomised double blind, placebo-controlled, multi-centric parallel arm trial of 6 months (three months treatment and three months observation period) with 14 days run-in period. The primary outcome is a composite of the changes in the TSS and SNOT-22 over 3 months from baseline with area under the curve and changes over 3 months in the Sinus Nasal Outcome Test 22 (SNOT-22) from baseline. Prescription shall be made as per the homoeopathic principles. Efficacy data will be analysed in the intention-to-treat population.
Discussion: This trial will help to evaluate the efficacy of homoeopathic individualised treatment using LM-potencies versus placebo in patients suffering from CRS as per the homoeopathic dictum.

Keywords: Chronic rhinosinusitis, Computerised tomography scan, Individualised Homoeopathy, Placebo, Fifty Millesimal Potency

BACKGROUND

Chronic rhinosinusitis (CRS) is characterised by inflammation of the nasal mucosa and paranasal sinuses of at least 12 weeks duration.[1] The cause of CRS is multi-factorial: Anatomic, genetic and environmental, leading to vicious cycle of infection, swelling and blockage.[2] It is the leading cause of general ill health and is considered the fifth most common disease treated with antibiotics.[3] The treatment of CRS remains an unmet need. A wide range of medical/surgical therapies has been used to treat it. Medical therapy includes antibiotics, corticosteroids, decongestants, antihistamines, mast-cell stabilisers, anti-leukotrienes, nasal douching, immunotherapy and reduction of environmental factors.[2] Nasal saline irrigation (both as

a sole modality and as an adjunct to medical treatment) is found to be beneficial.[4] Surgical treatment is reserved for refractory cases only.[5] However, overuse and inappropriate selection of antibiotic drugs are associated with increased drug resistance for respiratory pathogens leading to chronic disease and increased treatment costs.[6] Because of the heterogeneity underlying its pathology, no treatment regimen exists for its management.[7]

Homoeopathic medicine (s) are reported to cause improvement in a range of chronic and recurring pathologies and especially respiratory disorders.[8,9] It has been observed that patients seeking homoeopathic treatment had a better overall outcome compared to patients on conventional treatment[10]. A study conducted by CCRH on sinusitis showed positive results[11] but it lacked proper investigations. Another study by Witt *et al*.[12] not only showed improvement in symptoms related to CRS but also in quality of life. Further, the observational study by Nayak *et al*.[13] not only showed improvement in symptoms but also showed negative x-ray findings. The above observational studies reflect positive effects of Homoeopathy. However, to evaluate the efficacy of individualised Homoeopathy, a randomised, double blind, placebo-controlled, multi-centric parallel arm trial is carried out.

STUDY OBJECTIVES

Primary objectives

To evaluate changes in Total Symptoms Score (TSS) and Sino-Nasal Outcome Test -22 (SNOT-22).

Secondary objectives

To evaluate changes in SNOT 22 at end of the trial, changes in Lund and Mackay staging of CT scan, rhinoscopy grading, absolute eosinophil count, global assessment by investigator and patient, and number of acute exacerbation of CRS (for frequency, duration and intensity) as per TSS scale compared to placebo.

METHODS/DESIGN

Study design

This multi-centric study shall be carried out at four centres of CCRH as a randomised, double blind, placebo controlled trial with three months treatment and three months observation. At each study centre, a consultant, an ENT specialist shall be engaged for grading the rhinoscopy, TSS and SNOT score, and to help the investigator as and when required.

Eligibility criteria

Patient's eligibility is confirmed by the study investigators according to the inclusion and exclusion criteria mentioned in Table 1.

Allocation

The study is a prospective, randomised, double-blind, placebo-controlled, multi-centric parallel arm trial. Both the investigators and participants will be blinded to the group allocation. The trained pharmacist shall dispense medicines to Homoeopathy or placebo group according to a randomised assignment sequence generated by http://www.randomizer.org/and with the code 1 or 2 chosen by the study's coordinator. The randomisation sequence (one set of 30 non-unique numbers, ranging from 1 to 2, unsorted) was recorded and sent to the pharmacist at the start of the study. Only the chief coordinator and the pharmacist had access to the code of the randomised sequence during the study. After each patient completes the 6-month trial (or in emergency interventions—clinical worsening, disturbing adverse effects, if any), the pharmacist

Table 1: Eligibility criteria

Inclusion criteria

- Age group between 18-60 years from both genders
- Presence of two or more symptoms one of which should be nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip): ± Facial pain/pressure, ± reduction or loss of smell for >12 weeks with validation by interview. (as per European position paper on Rhinosinusitis and Nasal Polyps)
- Written informed consent
- Patients who can act in accordance with the protocol

Exclusion criteria

- Patients who are not adequately symptomatic
- Patients with serious underlying medical condition (e.g., Severe renal or hepatic disease)
- Patients with history of malignancy
- Patients taken any medication prior to entry into the study (can be enrolled after wash out period of 15 days)
- Patients taken topical steroids within 4 weeks before the study therapy (can be enrolled after wash out period of 1 month)
- Patients with atrophic rhinitis
- Patients with complications of chronic rhinosinusitis
- Patients with significant psychological problems as per the investigator
- Pregnant women and lactating mother
- Patients who do not give informed consent
- Patients having of underlying immune deficiencies, cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease, diabetes mellitus, neoplasia or fungal sinusitis
- Systemic diseases preventing participation in the study and medical and/or surgical treatments influencing the study as deemed by the investigator
- No prior paranasal sinus, nose surgery

CRS: Chronic rhinosinusitis

will inform the coordinator about Homoeopathy group or placebo group without disclosing the code.

Interventions

Each patient shall be given individualised homoeopathic medicine/placebo.

Homoeopathy group

Following inclusion, the patients shall go through a homoeopathic anamnesis with the investigator at each centre followed by repertorisation of the case to arrive at a group of medicines. However, final selection of medicine is to be made in consultation with Materia Medica. Homoeopathic LM-potencies will be procured from Good Manufacturing Practices certified company ranging from LM 1 to LM 30. To begin with, all the prescription will start with LM1 and shall move to higher potencies. The pharmacist will be oriented about preparation and dispensing of medicine as per homoeopathic principles. After receiving the prescription of investigator, the medicine was prepared as follows: One globule (poppy-seed size) of the medicine in LM potency to be dissolved in 120 ml of distilled water containing 2.4 ml (2% v/v) of dispensing-alcohol premixed in it, followed by ten uniformly forceful downward strokes given against the bottom of the phial. This solution shall be given to the respective patient with the instructions regarding the dosage as per the advise of the the investigator.

Control group

Patients randomised to this group shall receive placebo in similar manner to that of homoeopathic group; however, it would constitute unmedicated poppy-size sugar globule impregnated with dispensing alcohol, and any change triggered after administration (improvement/deterioration) will be followed by placebo only.

Rescue remedy

Before enrolment, it shall be ensured that patient is not taking any medication for a period of 14 days prior to enrolment in the trial i.e. in the run-in-period which shall help to assess for predominance of symptoms. If a patient is having Adverse Event-Chronic Rhino Sinusitis during the trial period, a symptom reliever such as saline nasal spray can be used in both the groups as a rescue remedy according to the need of each case.

Outcome

Primary outcome measures

The primary outcome is a composite of the changes in the TSS over 3 months with area under the curve and changes over 3 months in the Sino Nasal Outcome Test - 22 (SNOT-22) from baseline.

Secondary outcome measures

- Change in SNOT-22 (at 6 months)
- Changes in nasal endoscopy (at 3 months, 6 months)
- Changes in CT scan (at 3 months)
- Changes in absolute eosinophilic count (AEC) at 3 months
- No. of AE-CRS during observation period supported by rhinoscopic findings
- No. of AE-CRS (FDI) in between groups and
- Changes in global assessment by patient and physician at 3 months and 6 months.

Study duration

6 months for enrolment + 3 months treatment + 3 months observation period + 6 months for data analysis and manuscript preparation. The flow diagram of time line is given in Figure 1.

Sample size

The sample size was calculated keeping in view the outcome of the earlier observational study on chronic sinusitis by the Council (October 2005-March 2010).[14] The effect size in the previous study was found to be 0.8. Therefore, in this present study, using effect size of 0.8, with power 95%, $\alpha = 0.05$, intervention: Placebo: 1:1, the sample size calculated to be 42:42. Therefore, 84 samples were required. As the trial is multi-centric (4 centres) and for equal distribution among 4 centres, the sample size divisible by 4 was rounded up to 12:12 keeping the ratio intact. Further, with 15% of dropouts, the total sample size was rounded to 15:15 per centre. Thus, 120 patients shall be enrolled in the study.

Data collection

Data shall be collected at baseline from enrolled patients including demographics and past medical history, by the investigators at each centre. All information as mentioned will be recorded in pre-designed Case Record Form (CRF), original reports of investigations will also be documented. TSS and SNOT Forms will be filled by the patients. The consultant ENT will help in interpretation of the investigations and will be recorded in CRF. Any adverse event received will be noted and the coordinator will request additional details, specific to the nature of the event.

Data management

The information of all patients screened and enrolled shall be recorded. The case history of each enrolled case is to be recorded in the CRF and the relevant annexure pertaining to baseline assessment, TSS, SNOT-22,

		STUDY PERIOD							
	Enrolment	Allocation	Post-allocation in month						Close-out
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	t_x
ENROLMENT:									
Eligibility screen CT scan for positive CRS Total symptom score[TSS] Run-in phase for 14 days to check for persistence of symptoms	X								
Informed consent	X								
Allocation		X							
INTERVENTIONS:									
[Homeopathy]			←	—	→				
[Placebo]			←	—	→				
Observation period						←	—	→	
ASSESSMENTS:									
[List Baseline variables]									
TSS	X	X							
Sino nasal outcome test - 22 [SNOT22]	X								
Lund and Mackay staging for CT scan	X								
Lund and Kennedy for rhinoscopy	X								
Absolute eosinophil count	X								
[List outcome variables]									
TSS- every day for three months			X	X	X				X
SNOT-22 fortnightly			X	X	X	X	X	X	X
Lund and Mackay staging for CT scan					X				
Lund and Kennedy for rhinoscopy					X			X	X
Absolute eosinophil count					X				
Number of AE-CRS						X	X	X	X
Global health assessment by investigator	X				X			X	X
Global health assessment by patient	X				X			X	X
[List other data variables] Adverse events			X	X	X	X	X.	X	

Figure 1: Time line and schedule of enrolment, intervention, assessments

CT scan, changes in endoscopic grading, changes in bio-marker (AEC), global assessment by the investigator and patient, AE-CRS reporting form and details of medicine dispensing shall be entered and maintained.

Statistical methods

Efficacy data will be analysed in the intention-to-treat population. Continuous variables will be summarised using number of observations, median (inter-quartile range) or mean (SD) depending on variable distributions, whereas categorical variables will be summarised by the number and percentage of events. For primary outcome measure, area under the curve at 3 months shall be considered for TSS. Repeated measures shall be undertaken for SNOT-22, *t- test* will be carried out for CT scan, rhinoscopy and AEC, and other statistical tools, as appropriate, shall be used.

Regulatory and ethical considerations

The trial is approved by the Ethics committee of Central Council for Research in Homoeopathy. This study is to be conducted according to standards of Good Clinical Practice of India and in accordance with the requirements of the Declaration of Helsinki.

Protocol amendment

At the designing stage, endoscopic grading for CRS was recommended. However, due to feasibility problems and common consensus of consultants engaged in the trial, rhinoscopy was used for grading of sinusitis. The allocation of intervention, a priori it was designed to allocate in the ratio of Homoeopathy: Placebo=2:1. The effect size in the previous study was found to be 0.8. Therefore, in this present study, using effect

size of 0.8, with power 95%, α =0.05, intervention: Placebo=2:1, the sample size calculated to be 63:31. Therefore, 94 samples will be required. As the trial is multi-centric (4 centres), for equal distribution among 4 centres, the sample size divisible by 4 rounded up to 70:35 keeping the ratio intact. Further, with 10% of drop outs the total sample size was rounded to 20:10 per centre. Therefore, 120 patients were required for enrolment but allocation was done in the ratio of 1:1.

DISCUSSION

Several observational studies[10-13,14] and controlled trials with complex Homoeopathy[15-22] have shown positive outcome in respiratory complaints. However, for the first time this trial evaluates the efficacy of individualised Homoeopathy in chronic rhinosinusitis. Standard guidelines such as CONSORT[23] guidelines for reporting randomised trials with parallel groups, the reporting data on homoeopathic treatments (RedHot)[24] supplement to CONSORT and SPIRIT[25] guidelines are followed.

A long-term observational study conducted by Sharma *et al*.[11] on sinusitis with 394 followed-up patients showed complete cure in 138 patients, with no relapse after a follow-up period of one year. Another study by Witt *et al*.[12] included 134 adults showed relevant improvements persisting for 8 years in patients seeking homoeopathic treatment because of sinusitis. Further, in a short-term multi-centric observational study among 550 chronic sinusitis patients by Nayak *et al*.[13] the patients showed symptom relief along with reversal of pathology through X-ray findings after homoeopathic treatment.

In all the above-mentioned studies, homoeopathic medicines were found to have a positive role in treating a chronic condition such as sinusitis. However, control groups were either lacking or the control group was a complex Homoeopathy. In the present study, we attempted to incorporate these, so that a definite outcome can be observed.

Chronic sinusitis is amenable to homoeopathic intervention; individualisation as per homoeopathic principles is applied, expert involvement throughout the study design reflects support of homoeopathic practitioners, validated questionnaire *i.e.* TSS and SNOT-22 would address the main outcome measure reflecting the key effects expected of the intervention and will help in detecting change. Further, earlier study results by Nayak *et al*.[14] showed marked change in follow up of three months, which was considered for this design. The methodology adopted here is based on expert opinion and can be extended to day-to-day clinical practice by homoeopathic practitioners. Thus, it concurs with the Model Validity of Homoeopathic Treatment (MVHT) developed by Mathie *et al*.[26] This methodology can be assessed for almost perfect concordance with the six judgmental domains enabled MVHT.

We are optimistic that the trial has achievable enrolment targets and shall answer an important question in this emergent field.

Trial status

The data analysis is in progress and the result will be published soon.

COMPETING INTERESTS

The authors declare that they have no competing interests.

CONTRIBUTIONS

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चिरकालिक नासिका विवरशोथ के उपचार में होम्योपैथिक औषधियों के प्रभाव का मूल्यांकन करने के लिये एक यादृच्छिक, डबल ब्लाईंड, प्लासिबो नियन्त्रित बहुकेन्द्रीय समान्तर भुजीय परीक्षण

सारः

पृष्ठभूमि एवं तर्कः चिरकालिक नासिका विवरशोथ रोगियों के जीवन गुणवत्ता और कार्य उत्पादकता में ह्रास करने वाली एक मुख्य बीमारी है। परिषद् द्वारा पूर्व किये गये अवलोकनार्थ अध्ययनों ने सकारात्मक परिणाम दिये। इस प्रोटोकॉल को यादृच्छिक नियन्त्रित व्यवस्था में प्लासिबो की तुलना में होम्योपैथिक हस्तक्षेप की उपयोगिता का पता लगाने के लिये तैयार किया गया।

उद्देश्यः प्राथमिक उद्देश्यः (होम्योपैथी + प्लासिबो) अध्ययन के लिए दो समूहों में पंजीकृत किये गये कुल लक्षण स्कोर व एसएनओटी–22 का मूल्याकंन करना है। **द्वितीय उद्देश्यः** परीक्षण के अन्त में एसएनओटी–22 में परिवर्तन, सीटी स्केन लुण्ड व मैके की रफ्तार में परिवर्तन, रिहनोस्कोपी स्वरण, पूर्ण इओसिनोफिल संख्या, अन्वेषक व रोगियों द्वारा वैश्विक मूल्यांकन करना/टीएसएस पैमाने के अनुसार सीआरएस के तीव्र लक्षणों (बारम्बारता, समयावधि एवं तीव्रता) प्लासिबों के साथ तुलना की गयी।

सामग्री एवं विधियाँः यह एक यादृच्छिक, डबल ब्लाईंड, प्लासिबो नियन्त्रित, बहुकेन्द्रीय, सामान्तर श्रृंखलीय 14 दिन चलाने में अवधि के साथ छः महीने (तीन महीने उपचार व तीन महीने अवलोकनार्थ) का परीक्षण है। प्राथमिक परिणाम टीएसएस व एसएनओटी–22 पर 3 महीने के बाद उस अवस्था क्षेत्र के साथ आधारभूत तरीके से समग्र परिवर्तनी है। उपचार होम्योपैथी के सिद्धान्तो के अनुसार किया जाता है। प्रभावशील आँकडे जनसंख्या के उपचार के लिये विश्लेषित किये जायेगें।

चर्चाः यह परीक्षण होम्योपैथिक आँकडो के अनुसार सीआरएस रोगियों में व्यक्तिगत होम्योपैथिक उपचार की LM पोटंसी के विरूद्ध प्लासिबों की प्रभाविता का मूल्यांकन करने में सहायक होगा।