Efficacy of individualized homoeopathic treatment of chronic suppurative otitis media: double-blind, randomized, placebo-controlled trial

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Abstract

Background: Chronic Suppurative Otitis Media (CSOM) accounts for 28,000 deaths worldwide and a disease burden of over 2 million Disability Adjusted Life Years (DALYs). Most approaches to treatment have been unsatisfactory or are very expensive and difficult. Homoeopathy is a frequently consulted Complementary and Alternative Medicine (CAM) modality for the CSOM patients; however, scientific research has so far not provided evidences enough to support their efficacy or effectiveness. In this trial, we intend to evaluate the efficacy of IH in comparison with placebo in treatment of CSOM.

Methods/Design: In this prospective, double-blind, randomized, parallel arm, placebo-controlled trial, patients diagnosed with CSOM will be randomized in 1:1 ratio to one of the two interventions as Group 1: IH and Group 2: Placebo. The outcome measure being used is the Chronic Otitis Media Outcome 15 (COMOT-15) questionnaire. The study endpoint is 6 months. All outcome scores will be obtained at baseline, after 3 and 6 months. The trial will require 142 patients in order to achieve 80% power for the specified endpoint. In accordance with CONSORT/ReDHoT guidelines, all comparative analyses will be conducted on intention-to-treat basis using SPSS.

Discussion: The outcomes from this trial will generate efficacy data of IH in treatment of CSOM.

Trial registration: CTRI/2018/04/013235; UTN: U1111-1212-2819

Keywords
Chronic suppurative otitis media; Homoeopathy; Placebo; Randomized Controlled Trial
INTRODUCTION

Chronic suppurative otitis media (CSOM) is the result of an initial episode of acute otitis media (AOM), followed by chronic infection of middle ear and mastoid mucosa and is characterized by a persistent discharge from the middle ear through a tympanic perforation \[1\]. It is an important cause of preventable hearing loss, particularly in the developing world. Although there is no consensus on the duration of symptoms, generally long lasting infection and irreversible mucosal damage over 3 months is accepted as CSOM in clinical practice \[2, 3\].

The global burden of illness from CSOM involves 65-330 million individuals with draining ears, 60% of whom suffer from significant hearing impairment. CSOM accounts for 28,000 deaths and a disease burden of over 2 million DALYs \[4\]. Over 90% of the burden is borne by countries in the South-east Asia and Western Pacific regions, Africa, and several ethnic minorities in the Pacific rim \[4\]. The infection may occur during the first 6 years of a child’s life, with a peak around 2 years \[4\]. In CSOM, the bacteria may be aerobic (e.g. Pseudomonas aeruginosa especially; also Escherichia coli, Staphylococcus aureus, Streptococcus pyogenes, Proteus mirabilis, Klebsiella species) or anaerobic (e.g. Bacteroides, Peptostreptococcus, Propionibacterium) \[4\]. There are various potential complications and sequel of COM such as, hearing loss, ear drainage, facial nerve paralysis, vertigo, and meningitis. These symptoms may more or less compromise the quality of life. It is associated with significant functional limitations of hearing. This frequently results in communication problems impeding social interaction and professional life. In patients with severe hearing loss even a withdrawal from social activities can be observed frequently. In addition, further symptoms of CSOM such as persistent discharge from the ear, pain or frequent doctor visits may result in an impairment of the patients. In cases of cholesteatoma, which represents the most dangerous type of CSOM, complications like facial nerve paralysis, meningitis, or encephalitis may develop and potentially threaten the patient’s life. Most approaches to treatment have been unsatisfactory or are very expensive and difficult \[4\].

After extensive searches into electronic and different bibliographic databases up to 2017 and removing duplicate (repeat) publications, 15 studies \[5-19\] in homoeopathy were identified that were conducted on ear disorders: 14 on otitis media and 1 on tinnitus; 7 were peer-reviewed papers, rest non-peer-reviewed; 10 used individualized homoeopathy, 4 complex (including homotoxicological remedies), and 1 non-individualized, standardized remedy; 5 were observational trials, rest 10 were controlled studies. Thus majority of the studies revealed promising role of homoeopathic treatment in otitis media. However, the focus was principally on acute otitis media; and CSOM remained under-researched. This study presents the first randomized trial using the COMOT-15 evaluating the efficacy of IH treatment over placebo in CSOM.

Aims and objectives:
1. To evaluate the efficacy of IH medicines in comparison to placebo in treatment of CSOM
2. To compare changes in the COMOT-15 scores between groups
3. To ascertain and shortlist the most frequently indicated homoeopathic medicines in treatment of CSOM

METHODS / DESIGN

Study design: Prospective, double-blind, randomized, placebo-controlled, two parallel arms trial with a 6 months’ duration for each patient.

Trial registration: The study protocol is registered prospectively in Clinical Trials
Study setting: Outpatients or inpatients of National Institute of Homoeopathy (NIH)

Selection of samples: Samples will be selected as per below mentioned eligibility criteria from the patients visiting the NIH outpatients or admitted inpatients. Absence of any controlled trial of similar design precluded calculation of standardized difference (effect size) and sample size. Also, relevant data on COMOT-15 scores were not available for population of West Bengal. In a recent study, the mean (± standard deviation) of COMOT-15 scores of 100 patients diagnosed with CSOM was reported to be 25.4 (± 7.17) in south India [20]. We assume 25% and 10% reductions in the mean COMOT-15 scores in the verum and control groups respectively. Thus the assumed means and standard deviations of the verum and control groups become 19.05 ± 7.17 and 22.86 ± 7.17. Effect size (Cohen’s d) was calculated to be 0.531. Hence, keeping α = 0.05 and power (1 – β) = 0.80 (minimum recommended), and allocation ratio of 1:1, to detect a significant difference between two independent means (two groups) of COMOT-15 scores through unpaired t test, calculated sample size becomes 114. Keeping a provision for 25% drop-outs, the target sample size becomes 142 (verum: 71, control: 71).

Inclusion criteria:
1. Age 18-70 years
2. Both sexes
3. Symptomatic for last 3 months
4. Diagnosed to be suffering from CSOM by the consultant ENT surgeon
5. Standard therapy for CSOM, if ongoing, discontinued for at least 1 month
6. Providing written informed consent
7. Literate patients: ability to read English or Bengali

Exclusion criteria:
8. CSOM with cholesteatoma
9. Patients who are too sick for consultation
10. Patients unable to read patient information sheets, and not giving consent to take part
11. Major ear surgery in last 6 months
12. Diagnosed cases of unstable mental or psychiatric illness or other uncontrolled or life-threatening illness affecting quality of life
13. Pregnant women and lactating mothers
14. Substance abuse and/or dependence
15. Self-reported immune-compromised state, and
16. Undergoing any treatment for any chronic disease within last 6 months.

Criteria for discontinuing or modifying allocated interventions: Patients can be excluded from further participation within the study or withdraw themselves without having to provide any further reasons. Possible reasons for this therapy dropout are expected to be:
1. Withdrawal of the patient’s consent
2. Consumption of drugs or, rather, medications which are not permitted during the duration of the clinical study
3. Deficient compliance of patients after the evaluation of the examining physician (regular and specified consumption of study medication)
4. A newly occurring condition which influences the efficacy of the study investigation or is contra-indicative to the intake of study medication or which needs to be treated with a medication which is not permitted as a concurrent medication during the study
5. Retroactive appraisal of either unfulfilled inclusion criteria or fulfilled exclusion criteria after the decision of the examining physician/leader of the clinical study

6. Medically necessary transfer of the patient to a different department or hospital during the study phase

7. Unexpected findings which make the continuation of therapy from an ethical or medical point of view unjustifiable; the decision will be made by the concerned physician

The complete study can be discontinued prematurely if it is perceptible early on that it cannot fulfill the aforementioned inclusion criteria. This includes:

1. The necessary recruiting numbers cannot be achieved
2. There are serious violations of the protocol
3. The documentation is incomplete or was deliberately filled out incorrectly and legal or ethical instructions are not met

**Randomization:** Permutated block randomization method will be adopted to generate 14 blocks of 10 random numbers \(14 \times 10 = 140\) and another block of 2 random numbers (total 142) to maintain 1:1 distribution ratio. Random sequence (1 and 2 for either of medicine or placebo) will be generated by a third party who will not be allowed to influence the study in any way. This chart will be made available to the pharmacist in strict confidentiality and will never be disclosed to the patients or doctors under any circumstances. The allocated code will be maintained till the end of the trial.

**Blinding:** Participants, the principal investigator and the co-investigators, the outcome assessors, and the pharmacist will remain blinded to the identity of the two treatment groups until the end of the study. Concealment will be maintained by identically coded containers having alike vials of either medicine or placebo. Unblinding of individual participants through the investigator occurs in cases of SAEs.

**Intervention:**

- **Experimental arm:** Indicated homoeopathic medicines will be administered in centesimal potencies and in individualized dosage, as decided appropriate to the case or condition. Each dose consists of 4-6 cane globules no. 20 moistened with the indicated medicine (preserved in 90% v/v ethanol); to be taken orally on clean tongue with empty stomach; dosage and repetition depending upon the individual requirement of the cases. Duration of therapy: 6 months.

- **Comparator arm:** Placebo, indistinguishable from verum, will be administered in individualized dosage orally on clean tongue with empty stomach for 6 months. Each placebo dose will consist of 4-6 cane sugar globules no. 20 moistened with 60º OP ethanol. Duration of therapy: 6 months.

The homoeopathic medicines and placebo are provided by HAPCO® as bulk product. Both medicines and placebo are repacked in identical glass bottles and labeled with code, name of medicine and potency. These were dispensed according to the randomization list provided to the pharmacist.

**Selection of tools:**

1. Standardized data recording proforma
2. Repertorization software [RADAR®, version 10.0.028 (ck), Archibel 2007, Belgium]
3. COMOT-15 questionnaire (Bengali version)

**Brief of procedure:** Following preliminary screening using inclusion criteria and detailed screening using specified exclusion criteria, eligible patients will be recruited in
the trial. Following that, outcome data (baseline COMOT-15 questionnaire score) will be obtained. Coded identical containers will be used. Final selection of the single individualized medicine will be based on case taking in adherence with the standard homoeopathic guidelines, analysis and evaluation of symptoms, miasmatic diagnosis, framing symptom totality, repertorization and consultation with Homoeopathic Materia Medica. Individualized dose will be selected on the judgment of susceptibility of the patients. Subsequent prescriptions will be generated according to Kent’s observations, second prescription, and relevant homoeopathic principles and will be recorded in follow-up sheets.

Outcome assessment: The outcome measure is the English and Bengali version of the COMOT-15 questionnaire \cite{2}. It is a reliable, valid and sensitive instrument for measurement of HR-QOL of COM patients and is recommended to be used in otological outcomes research. COMOT-15 showed an excellent reliability with high internal consistency (Cronbach's alpha from 0.89 to 0.91) and high retest reliability coefficients (all r more than 0.8). Content validity was determined by a study of the literature. COMOT-15 could distinguish COM patients from healthy subjects. Global assessment of impairment of HR-QOL by COM correlated very well with the scores of COMOT-15. However, the responsiveness of the COMOT-15 questionnaire was low. Before this trial was initiated, the COMOT-15 questionnaire underwent standardized forward-backward translation into local vernacular Bengali, was checked for face and content validity, and subjected to pilot testing and thereafter formal psychometric validity and reliability testing. Subsequently, the authors conducted an open observational trial [Trial registration CTRI/2017/03/008081; Universal Trial No. U1111-1193-8350] to examine the possible effects of individualized homoeopathic medicines in 100 patients suffering from CSOM at Mahesh Bhattacharyya Homoeopathic Medical College and Hospital (manuscript under preparation and still unpublished).

Data collection: The outcomes will be assessed at baseline, after 3 months, and after 6 months. A specially designed Microsoft MS Office Excel 2007 spread sheet (master chart) will be used for data extraction and shall be subjected to statistical analysis.

Statistical techniques and data analysis: It will follow the intention-to-treat (ITT) approach; i.e. every included patient will enter the final analyses. Missing values will be imputed and replaced. Descriptive data (categorical and continuous) will be presented in terms of absolute values, percentages, mean, standard deviations (sd), confidence intervals (CI), etc. as appropriate. The groups will be checked for comparability of socio-demographic characteristics at baseline. Parametric or non-parametric inferential tests will be used to detect group differences as per normality or non-normality of distribution of data respectively. P values will be set at less than 0.01 two-tailed as statistically significant. SPSS® IBM® Inc., version 20 for Windows shall be used for statistical analysis. Aside from the analysis of all randomized patients, a per-protocol analysis will also be carried out which is supposed to indicate which effect sizes can be reached under optimal circumstances. In the per-protocol sample, all patients will be included who fulfill all study requirements.

Ethical issues: Intercurrent illness, adverse or serious adverse event(s), if any, will be recorded and treated accordingly as per homoeopathic principles irrespective of the allocated codes, or if non-responding, then the patient shall be referred for conventional treatment. Prior to enrolment, each patient will be provided with a patient information sheet in local vernacular Bengali detailing
the objectives, methods, risks and benefits of participating, and confidentiality issues. Subsequent to that, written informed consent shall be obtained. Approval is already taken from the institutional ethics committee (IEC) prior to initiation [5-23/NIH/PG/Ethical Comm. 2009/Vol 5/2687 (A/S); March 28, 2018]. The study shall be performed under the constant supervision of the IEC. This study is in compliance with the Helsinki Declaration and with the International Conference on Harmonization (ICH) – Good Clinical Practice. Protocol amendments, if necessary will be submitted to the ethics committee and implementation will be done after approval.

Study flow diagram:

DISCUSSION & CONCLUSION

Despite the fact that homoeopathy has a long tradition in the complementary treatment of patients and is part of the medical curriculum in many European universities, there is an ongoing debate on its efficacy, effectiveness and credibility. Thus, more robust clinical studies with clear and relevant endpoints are needed to substantiate the evidence base from primary to critical care. This study examines the efficacy of individualized homoeopathic medicines over placebo in CSOM in randomized design and prospectively for the first time toward generating clinical evidence. The use of homoeopathic medicines in CSOM is quite popular; however, scientific papers are sparse. This is a uni-centric study in a homoeopathy hospital. The protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [21] and TIDieR (Template for Intervention Description and Replication) checklist [22]. Reporting of the study results will adhere to the criteria for reporting individualization in homoeopathy [23], the RedHot (homoeopathy specific CONSORT) statement [24] and model validity of homoeopathic treatment (MVHT) [25].

Should the main outcome of the trial be positive, the qualitative element of the study will provide insights into individualized homoeopathic treatment of CSOM. Publication of results in a peer-reviewed and indexed scientific journal and presentation at scientific meetings is planned. Due acknowledgement and/or authorship will be given to them who have participated in the proposal development and data analysis at the end of the paper with their specific contribution to the study. Authorship credit shall be based on substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published.

Trial status: At the time of initial manuscript submission, recruitment had already started (April 2018); and is ongoing.

Conflict of interest: The authors declare that they have no competing interests.

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Authors’ contributions: RG conceived and designed the study and remains the principal investigator. DP and AC are the co-investigators.
MK and SS wrote the study protocol and are responsible for statistical analysis. AB and SSA are responsible for data compilation and management. RG, PM, and KB are responsible for data collection and the homoeopathic part of the study. SS drafted the manuscript. All authors reviewed and approved the final manuscript.

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REFERENCES


