STUDY PROTOCOL

Study setting and Design

The study was a randomised, placebo-controlled, parallel-arm trial conducted as follows:

1. The outpatient clinic for hypertensive patients at Dr M. L. Dhawale Memorial Homoeopathic Institute and Hospital, Palghar.
2. Shree Mumbadevi homoeopathic hospital, outpatient department, Vile Parle, Mumbai.
3. Private clinic at Andheri, Mumbai
4. Polyset Plastics factory at Daman.

The study started on 1st January 2015 and culminated on 31st July 2018, according to the Reporting Data on Homoeopathy Treatments (ReDHoT) (Dean et al., 2007) guidelines.

Screening and enrollment followed by intervention and follow-up for six months (CONSORT diagram).

The study protocol was per the Helsinki Declaration on Human Experimentation (WHO, 2001) and Good Clinical Practice (EMEA, 2002) in India.

Clearance was obtained from the Institutional Ethics Committee. Consequently, each participant was verbally explained about the study and was also given a patient information sheet in the language s/he understood. Written consent was obtained from them, along with the signature of the witness present. However, they were free to withdraw from the study at any point in time.

Operational definitions of various terms

1. **BLOOD PRESSURE: (BP)**

Lateral pressure exerted by blood on the arterial wall while flowing through it.

2. **HYPERTENSION: (HT)**

The American Society of Hypertension (ASH) Writing group, as updated, defines hypertension as follows:

Hypertension is a progressive cardiovascular syndrome arising from complex and interrelated aetiologies. Early markers of the syndrome are often present before blood pressure elevation is sustained; therefore, hypertension cannot be classified solely by discrete blood pressure thresholds. Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature and other organs, leading to premature morbidity and death.

The dividing line between normotension and hypertension was arbitrary. The current definition is the blood pressure above which the intervention has been shown to reduce the risk (Evans & Rose, 1971). It is well established that lowering even mildly raised pressures reduces morbidity and mortality from cardiovascular disease (Collins, Peto, MacMohan, Herbert, Fiebach, Eberlein et al., 1990).

Table 4.1 BLOOD PRESSURE CLASSIFICATION ACCORDING TO JNC 7

BP Classification	**SBP mm of Hg**	**DBP mm of Hg**
Normal	< 120	< 80
Prehypertension	120-139	80-89
Stage 1 Hypertension	140-159	90-99
Stage 2 Hypertension	≥ 160	≥ 100

1. **Essential Hypertension (EHT)**

Essential hypertension, also known as primary or idiopathic hypertension, is high blood pressure not explained by secondary causes, representing 95% of high blood pressure cases (Carretero & Oparil, 2000).

2. **STRESS:**

Stress is defined as a process in which environmental demands exceed an organism's adaptive capacity, resulting in psychological and biological changes that may place persons at risk for disease.

According to Neuman, a stressor is any relationship between the person and the environment appraised by the person as taxing.

Stress is the sum of the physical, mental and emotional strains or tensions on a person. Feelings of stress in humans is a consequence of synergy between individuals and their surrounding that are grasped as straining or exceeding their adaptive capacities and threatening their well-being (Definition of stress by the Gale Encyclopaedia of Mental Disorders (2003)).

4. **ANGER:**

Anger is an experiential state consisting of emotional, cognitive and physiological components that rapidly interact with and influence each other so that it tends to be experienced as a single phenomenon. It is an emotional state that consists of feelings that vary in intensity, from mild irritation or annoyance to fury and rage.

5. **STATE ANGER:**

State anger is a transitory emotional state or condition that consists of subjective feelings of tension, annoyance, irritation, fury and rage, and the autonomic nervous system's activation or arousal.

6. TRAIT ANGER:

Trait anger refers to relatively stable individual differences among people in the disposition to perceive a wide range of situations, such as annoying or frustrating and in the tendency to respond to such situations with marked elevations in state anger.

7. ANGER-IN:

Refers to individuals who frequently experience intense, angry feelings but tend to suppress them rather than express them verbally or physically.

8. **ANGER-OUT: -**

It is characterised by the frequent anger expressed in aggressive behaviours directed toward other people or objects in the environment. For example, slamming doors, pounding table-tops, assaulting the person or verbally in the form of insults, threats, criticism, and use of profanity.

9. **ANGER –CONTROL/REFLECTION:** It is characterised by a concerted attempt to constrain and control angry feelings and solve problems that focus on provocation.

10. CONSTITUTION:

Constitution has been defined as the inherited and acquired physical, emotional, and intellectual makeup of a person, revealing itself in the habit, basic emotional and intellectual inclinations, and how the individual reacts to internal and external stress factors.

11. SIMILIMUM:

The similimum is a remedy that has been mentioned in the materia medica after proving on healthy human beings to produce the closest matching set or cluster of individualised features in minimum effective potency required to generate curative action in the shortest time.

The remedy selected based on the totality of symptoms, the most appropriate remedy, in the requisite potency suitable to the patient, which is vital for evoking optimum response and a speedy recovery, is called similimum.

12. TOTALITY OF SYMPTOMS:

It is the outwardly reflected picture of the internally deranged vital force.

The peculiar, characteristic individualising features of the case taken into consideration in developing the image are called the totality of symptoms[365].

DESCRIPTION AND EXPLANATION OF THE PROCEDURES:

It is an experimental study that is the first of its kind in homoeopathic psychiatry; hence, it is a randomised controlled trial. Patients diagnosed with essential hypertension after satisfying the inclusion criteria were included in the study. A STAXI-2 based questionnaire was completed before starting the treatment and was subsequently filled after six months of treatment initiation. Along with the questionnaire, subjective and objective improvements and investigations were assessed.

All the patients were informed about the DASH diet and advised to follow lifestyle changes as per their individual requirements.

If the medical consultant advised, all patients were started on antihypertensive medication as per the standard protocol for managing essential hypertension. There were two groups of patients. One group was administered placebo and antihypertensive (wherever required), and the other group was administered constitutional homoeopathic medicine (along with antihypertensives if needed) after the case was duly processed.

Patients who were already on antihypertensive treatment were advised to continue the treatment.

Preparation of proforma/ case study

1. Patients diagnosed with essential hypertension by the physician or patients who came to the outpatient department and were found to have blood pressure values higher than desired were screened as per the special questionnaire prepared to evaluate preliminary details for essential hypertension. This questionnaire is attached to an annexure.
2. The case history was taken in a standardised case record used in a homoeopathic setup.
3. A STAXI-2 (Spielberg et al., 1988)-based questionnaire was used for anger assessment.
4. The Hindi version of STAXI-2, translated and validated by Dr Suneil Saini, was used for patients who did not understand English.

Since this type of study is undertaken first in homoeopathic psychiatry, no protocol testing has been performed.

Enumeration of population universe:

The population examined was from homoeopathic setups in western Maharashtra.

Sample size:

The effect size calculated from the study on HT conducted by CCRH (Baig et al., 2009) was 0.6 [SBP: 157.65 +/- 13.05 versus 143.41 +/- 12.41, Cohen's d=1.13, effect size = 0.5; DBP: 100.77 +/- 4.04 versus 89.13 +/- 7.75, Cohen's d = 1.88, effect size = 0.7; overall effect size = 0.6; calculated at UCCS557. The effect size (standardised difference) of 0.6, power of 90% and significance level (α) of 5%, were considered and the required sample size was determined to be 118 using Altman's nomogram. The targeted sample size came to 150 after keeping a provision for dropouts of approximately 27%. It was the size calculated for this study, such as ours.

Given no previous study on the efficacy of homoeopathic medicines on anger as an aetiological factor for EHT, and this being a pilot randomised control trial, we decided to keep patients' enrollment for two years. Each patient was studied for six months after the intervention with regular follow-up every two weeks. A total of 172 patients were enrolled after informed consent was obtained. The participants were divided into two equal arms by simple randomisation. One group was administered a placebo, and the other group was administered the individualised constitutional homoeopathic remedy (similimum) along with antihypertensive, wherever required, as per the treating physician's prescription.

Parameters used for identifying the population base:

1. The evaluation form was used to define the essential hypertension patiets ranging from 18 to 65 years of age and of both sexes.
2. STAXI 2 – STATE AND TRAIT ANGER EXPRESSION INVENTORY -2

To quantify the anger of patients. It was repeated after a six-month study period.

1. Blood Pressure measurements
2. Clinical history of hypertension

DESCRIPTION OF INDEPENDENT VARIABLES AND DEPENDENT VARIABLES:

Independent variables:

1. Anger
2. Age
3. Family history of essential hypertension
4. Excessive salt intake
5. Excessive alcohol intake
6. Tobacco consumption

7. Obesity
8. Diabetes
9. Hyperlipidemia
10. Hyperuricemia
11. Physical activity level
12. Financial or job strain
13. Strain in Interpersonal relationships as per their residential setting.

Dependent variable:

Blood pressure

Confounding (factors) variables:

1. Environment – incidents that increase the hostility or anger in patients
2. Antihypertensive treatment

The sampling technique used for obtaining the sample size:

Simple random sampling technique: This is an experimental study in which the action of individualised homoeopathic medicines was assessed by modifying the anger state trait.

Derivation of the sample in the study group and control group:

During the two-year study enrolment period, patients were screened for essential hypertension and were grouped into intervention (verum) and placebo groups by a simple randomisation procedure.

Inclusion criteria:

The study inclusion criteria consisted of patients:

- Suffering from essential hypertension (pre-hypertensives: SBP 120-139 mm Hg, DBP 80-89 mm Hg, stage I hypertensives: SBP 140-159 mm Hg, DBP 90-99 mm Hg; stage II hypertensives: SBP more than or equal to 160 mm Hg, DBP more than or equal to 100 mm Hg;
- Patients on antihypertensive treatment
- Aged 18-65 years
- Of both sexes
- The patients whose history, examination and routine investigations revealed no evidence of apparent secondary cause.

Exclusion criteria:

- Physical examination or routine investigations produced suspicion of a secondary cause for HT.
- Provisional or confirmatory diagnosis of secondary HT.
- Patients with uncontrolled Diabetes Mellitus or any uncontrolled endocrine disorders.
- Patients diagnosed with psychiatric disorders like schizophrenia or endogenous depression.
- Pregnant or breastfeeding mothers having HT.

Withdrawal criteria:

- Patients who develop uncontrolled hypertension during the study
- The patient's blood pressure did not respond to homoeopathic treatment within three months of commencing the treatment.
- Female patients who conceive during treatment

- Patients were given an option to withdraw from the study at any point in time without affecting their current treatment and without giving any reason. They could continue to receive treatment from their respective physicians in the outpatient department.

Discontinuation criteria:

- Patients reporting irregularly for follow-ups, who did not take homoeopathic medicines for more than four weeks and who did not complete the minimal 6-month follow-up
- Investigator's decision.

Intervention (Medicine) / Comparator (Placebo)

A range of homoeopathic potencies was used according to the requirements of the case. All the medicines used were manufactured by a Good Manufacturing Practice certified homoeopathy pharmaceutical company. They were prepared strictly, adhering to the regulations and instructions of the Homoeopathic Pharmacopoeia of India. Medicines in all forms and placebo were dispensed in the Good Clinical Practice environment. Each dose administered orally, either medicine (in centesimal potencies) or placebo, identical in appearance, consisting of medicated globules of size 35 or comparator placebo in identical vials or sacrum lactis powder either medicated with individual medicinal liquid or sacrum lactis liquid.

Specificity / sensitivity of the test/ procedure/ trial:

STAXI-2:

Spielberger's (1999) State-Trait Anger Expression Inventory -2 (STAXI-2) is a measure of anger experience and expression used to assess aggression and violence, given the close association between anger dysregulation and aggressive and violent behaviour. The STAXI-2 is one of the most widely used measures in both clinical and research settings (Novaco &

Taylor, 2004). There is psychometric support for its use in different cultures, including both Asian (Bishop & Quah 1998; Ghos & Sharma 2006) and Western populations (Lindqvist, Daderman & Hellstrome, 2003; Miguel-Tobal, Casado, Cano-Vindel & Spielberger, 2001; Muller, Bongard, Heiligtag & Hodapp, 2001).

It has reasonable reliability, internal consistency and constructs, content, concurrent, convergent, divergent and discriminant validity (Spielberger, 1999).

It measures the experience and expression of anger and is a 57-item self-report questionnaire. It consists of six scales and an anger expression index. It is a widely used scale for assessment, with the following dimensions:

State Anger (S-Ang): the intensity of angry feelings at the time of completion;

Trait anger (T-Ang)- a disposition to experience anger;

Anger Expression-Out (Ax-O)- the expression of angry feelings out;

Anger Expression-In (AX-I)- the suppression of angry feelings;

Anger Control-Out (AC-O): the prevention of anger expression toward other people or objects;

Anger Control-In (AC-I)- the control of suppressed anger and

Anger Expression Index (AX-index) is an overall index of the frequency of anger expression, regardless of direction.

Understanding these dimensions have significant therapeutic implications.

It has 57 statements divided into three parts. Multiple options follow each statement, and the subject has to choose the one that best describes him/her.

Part 1, which relates to state anger, consists of 15 statements that describe how a person feels currently with 4-point Likert-type options: *not at all, somewhat*, *moderately,* and *very much so*.

Part 2 consists of 10 statements describing how they generally feel or react and tap into trait anger. It also uses 4-point Likert-type responses: *almost never*, *sometimes, often* and *almost always*.

Part 3 consists of 32 statements related to how often individuals generally react or behave when they feel angry or furious. It provides a measure of anger expression and anger control and generates an anger expression index.

The raw scores generated were transformed into T scores from the normative scores given in the manual.

The subscales of the STAXI-2 are internally consistent (αs = 0.74–0.95) and have been validated against various indices of anger-related physiological arousal and other self-report measures of anger and hostility (Deffenbacher, 1992; Spielberger, 1999).

In this study, for patients who had difficulty understanding English, the Hindi version of STAXI-2 was used, which has been translated, standardised and validated by Dr Anuradha Navale and Dr Suneil Saini. Their permission was obtained for this study.

Calibration, validation and standardisation of the instrument:

To measure clinic BP self-measurement, an automatic digital monitor OMRON (Omron Corporation, Kyoto, Japan) was used, which meets the precision criteria established by the European Society of Hypertension (O Brien et al., 2001) and the British Hypertension Society (Coleman et al., 2006).

Measurement of blood pressure:

Blood pressure was measured in a sitting position with back supported, arm free of clothing and resting on a surface at heart level for at least five min, before measurement (Seedat et al.,

2006)[558]. The patient was requested not to talk during the blood pressure measurement (Burgess et al., 2011)[559] and asked not to smoke, consume caffeinated beverages, or not have food in the previous thirty minutes (Seedat et al., 2006)[558] of measurement.

At the initial consultation, blood pressure was measured in both arms, and in patients in whom differences were found, blood pressure was measured in the arm with the higher blood pressure. The blood pressure recorded was the average of two readings taken one minute apart. Additional readings were taken when the first two readings differed by more than five mmHg.

Study design:

A randomised control trial.

The study participants' hypertensive status was initially confirmed by taking the average of the measured BP twice on two separate occasions in two contralateral arms in a supine position during rest, using a digital blood pressure monitor throughout the study. Every case was subjected to detailed screening using a specified eligibility criterion, followed by recruitment in the trial. After recruitment, all patients underwent baseline assessments. The pre-study entry laboratory investigations were performed as follows:

CBC: complete blood count

BSF, PP: blood sugar fasting and postprandial

S. Creat.: Serum creatinine

S. Uric a.: Serum uric acid

Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, serum triglycerides, total cholesterol and HDL ratio

Urine routine analysis to rule out haematuria and proteinuria

ECG: Electrocardiogram

X-ray chest PA view

Abdominal ultrasonography

Data were extracted from the reports directly and independently.

Of 300 hypertensive patients assessed for eligibility criteria, 172 were enrolled. Patients diagnosed with essential hypertension after satisfying the inclusion criteria were included. A thorough homoeopathic case taking was performed for all patients. A questionnaire in the STAXI-2 scale was completed before starting the treatment and after the six-month study period. Their subjective improvement, objective improvement, and investigations, if required, were regularly assessed along with the questionnaire.

All patients in both groups were given the necessary DASH (Sacks, Svetkey et al. 2001)[521]diet, exercise and appropriate lifestyle modification advice along with insights about problems and harmful effects of anger.

Those patients, whom the medical consultant advised, started on antihypertensive medication as per the standard protocol for managing essential hypertension. One group of patients was administered a placebo, and another group of patients was administered Constitutional homoeopathic medicine after the case was duly processed.

Standardisation of the treatment:

Selection of Medicine:

The selection of medicine was guided by the totality of the presenting signs and symptoms based on the Principle of Similia after repertorisation. In cases where a non-repertorial approach is taken, an appropriate explanation was provided to justify the remedy's selection.

Selection of Potency and repetition:

For this, we followed the well-accepted rules of potency selection and repetition, as mentioned initially in the organon and later refined by other authors. The same summary is found in the book "Principles and Practice of Homoeopathy" Part 1 by Dr M. L. Dhawale, (Chapter 16)[31].

Change of Remedy:

The remedy can be changed under the following conditions:

1. No improvement in the patient
2. The appearance of new symptoms (without a feeling of general well-being) pointing toward another remedy.
3. Complementary / Follow-up remedy when the improvement process halts despite the repetition/change of potency.

Use of Antimiasmatic / Intercurrent prescription:

An intercurrent with a high potency may be prescribed when the patient's case history indicates a miasmatic load as a fundamental/dominant cause.

DATA COLLECTION:

- Screening for essential hypertension in OPDs.
- Patient enrolment in the study was according to Inclusion and Exclusion Criteria.
- Informed Consent
- The STAXI 2 (Annexure 4) scale was administered to all patients at the time of intake. The scale was translated into the local language (Marathi) from the Hindi version of STAXI-2, which was prepared, authenticated and validated by Dr Suneil Saini. Relevant permissions were taken from the copyright owners of both the English and Hindi versions of the STAXI 2 scale.
- A detailed case history from patients, relatives and attendants regarding the onset, duration and progress of the complaints were recorded according to standard case records from the respective institutes. The Anger Assessment Scale was applied to both study groups at the beginning and end of the study period.
- Along with case-taking, patients were advised to a salt-restricted (DASH) diet and exercise and were also made aware of the harmful effects of anger.

- Routine investigations such as CBC, BSF, BSPP, S. creatinine, lipid profile, S. uric acid, urine routine, X-ray chest, and ECG USG abdomen duly recorded to rule out secondary causes of hypertension.

ANALYSIS PLAN:

The data analysis includes:

- Estimation of Anger Assessment Scale
- Comparison of anger assessment ratings between the two groups and within each group (state, trait and expressions)
- Correlation of Anger Assessment ratings with Systolic and Diastolic Blood Pressure.

PARAMETER ESTIMATION:

- Anger assessment ratings on STAXI-2 should reduce significantly at the end of the study compared to the pre-test scores.
- Subjective Distress
- Objective Parameters:
    - Systolic & Diastolic Blood Pressure

STATISTICAL METHODS:

Statistical comparison was made at a difference of 5% of the significance level.

- Paired ‘t’ was used to assess the comparison before and after the treatment in the same patient and unpaired ‘t-test for group comparisons.

The intention-to-treat (ITT) population was subjected to statistical analysis. Comparable baseline characteristics and potential variables were matched to evaluate whether the samples originated from the same distribution and whether they differed statistically significantly.

Missing values were calculated using the maximum likelihood method of estimating the normal distribution's lambda parameter.

The data were checked for normal / non-normal distribution using descriptive statistics of skewness and kurtosis, and appropriate tests (parametric / non-parametric) were performed accordingly. The analysis was planned to be performed on demographic data and treatment outcomes to test the group differences using the independent *t-test*.

METHOD OF STUDY

- Each patient's clinical manifestation in terms of location, sensation, modality, concomitant, and life-space through detailed case taking was recorded.
- Each case was analysed in detail concerning the patients' complaints, personal characteristics, and family history.
- Studying the evolution of etiopathogenesis and progression in the development of essential hypertension
- Trait-State aspects of anger were measured through STAXI -2

Outcomes Measures:

The outcome measures were changes in systolic and diastolic blood pressure at a time of six months. The effect size was considered to lower systolic and diastolic BP by a minimum of 15 mm and 6 mm Hg, respectively. Thus, cases where this lowering in SBP and DBP was observed, were described as 'improved' and the rest were not improved'. The study endpoint was the lowering of BP following an intervention. The primary safety endpoint was any adverse event during the study in any of the groups. The stopping guidelines included a marked deterioration of health condition and constant increase in BP among subjects in either group,

continuous progress of the disease with the appearance of complications, and adverse events (if any).

RISKS AND BENEFITS:

The research studies quoted have shown that homoeopathic medicines are effective in treating hypertension. The risk of elevation of hypertension in homoeopathic treatment was taken care of with withdrawal criteria. The benefit of participating in the study was that patients contributed to generalised medical knowledge, lacking in this topic.

ETHICAL COMMITTEE APPROVAL:

It is attached as per the requirements.

Table – 4.2 Time Utilization Calendar

A	Date of Provisional registration for PhD	16/1/2014
B	Duration for preparation of the Study title, Study Protocol etc. to formulate the synopsis	Three months
C	Date of Submission of the synopsis to the Institutional Ethics Committee:	October 2014
D	Date of approval of the synopsis by the Institutional Ethics Committee	6/12/2014
E	Date of Approval of the synopsis by the MUHS	21/12/2014
F	Date from which the actual work started	1/1/2015
G	Whether the study was 'Single Observation' Study or 'Follow-up' Study	Follow-up study – randomized control trial-interventional type

H	Whether every case/ control/procedure/technique etc., was observed at a given specified, limited time span, or whether the work required more time? If so, the reasons therefore.	Every 2-weeks follow-up for six months study period
I	How much time was required per case / per procedure / per- standardization technique etc.?	One hour approximately
J	How many subjects/procedures/techniques were studied, how many times, at what intervals etc.	172 subjects, follow-up every 2-weeks for six months
K	The date on which actual work, i.e. data collection and recording of observations, was completed?	31/7/2018
L	Total Study Period dates	Two years seven months
M	The time required for compilation and analysis	Four months
N	Total Duration from	1/1/2015 to 27/2/2019