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STUDY PROTOCOL

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Efficacy and safety of ayurvedic intervention (*Sarpgandha Mishran*) vs amlodipine for Stage-I primary hypertension- study protocol for a prospective Double-Dummy, Double-Blind, placebo-controlled Randomized Clinical Trial

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Abstract

Background Hypertension presents as a modifiable risk factor for cardiovascular diseases, with approximately two-thirds of the global hypertensive population concentrated in low- and middle-income nations. *Sarpagandha Mishran* is an Ayurveda intervention utilized for the management of hypertension. The objective of the study is to assess the clinical efficacy and safety of *Sarpgandha Mishran* in the Management of Stage-I Hypertension.

Methods This clinical trial employs a prospective design characterized by a double-dummy, double-blind, placebo-controlled methodology being conducted at Cardiology Outpatient Department of the AIIMS, New Delhi. A total of 150 participants (75 per group), diagnosed with Stage-I essential hypertension will be randomized and allocated in a 1:1 allocation ratio, to either Ayurveda group or Conventional Care group. Participants in Group I will receive Ayurvedic intervention, *Sarpagandha Mishran* 500 mg capsules orally twice daily, in addition to a matching placebo of Amlodipine 5 mg capsules orally once daily. Group II will receive a matching placebo of *Sarpagandha Mishran* 500 mg capsules along with Amlodipine 5 mg capsules orally once daily. All participants will also be administered Hydrochlorothiazide 12.5 mg tablets orally once daily for a duration of 12 weeks. The primary endpoint of this study involves evaluating changes in SBP and DBP from baseline to week 12. Secondary outcome includes assessing changes in IL-6, Serum Pro-BNP, oxidative stress markers, lipid profile, and the SF-36 Health Survey Score. Safety assessments will be done through recording of AE/ADR and assessments of liver function tests and renal function tests parameters.

Discussion The present study is poised to furnish comprehensive insights into the clinical efficacy and safety profile of *Sarpagandha Mishran* in the management of Grade 1 hypertension. By adopting a rigorous scientific methodology, this investigation aims to contribute robust evidence that may significantly impact the formulation of future guidelines for integrative treatment protocols in hypertension management.

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Trial Registration The trial is prospectively registered with the Clinical Trial Registry of India [CTRI/2021/12/038589], dated 13.12.2021.

Keywords Integrative treatment, Hypertension, Ayurveda, Efficacy, Safety, RCT study

Protocol version:

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Names, affiliation, and roles of protocol contributors:

Dr. Babita Yadav, RO (Ay), CARI, developed the protocol and reviewed the article. Dr BCS Rao, AD (Ay) conceptualized the idea and developed the protocol in consultation with the investigators and approved the final version. The overall co-ordination of the study is dealt by them. Dr. D.S. Arya, Professor, Dept. of Pharmacology, AIIMS, New Delhi vetted the study design and conducted the study under his supervision as Investigator. Dr. Rajiv Narang, Professor, Dept. of Cardiology, AIIMS, New Delhi gave his expertise in designing, revision and finalization of the protocol. Dr. Sophia Jameela, RO (Ay), edited and reviewed the protocol and drafted the protocol article in consultation with the investigators and study coordinators. Dr. Shruti Khanduri, RO (Ay) actively involved in the conceptualization and finalization of the study interventions and reviewed the article. Dr. Sakshi Sharma, RO (Ay), coordinated the study as a co-investigator and reviewed the protocol and article. Dr. Drishya Dinesh prepared the zero draft of the protocol article and reviewed the literature. Ms. Arti Srivastava reviewed the literature and delt with the initial technical issues related to ethical clearance. Dr. Richa Singhal gave methodological inputs and is involved in handling the statistical part of the protocol including sample size calculation, randomization and plan of analysis. Dr. Richa Bhardwaj worked as Senior Research Fellow for 5 months delt with the technical issues related to the protocol finalization and provided logistical support. Dr. Bharti Gupta, Director, CARI, Delhi over all coordinated the project and provided scientific insights. and mentorship N. Srikanth, DDG, CCRAS, provided the overall guidance in conceptualization, finalization of protocol, methodological inputs and article review as the technical team head.

Name and contact information for the trial sponsor:

Central Council for Research in Ayurvedic Sciences, Jawahar LAL Nehru Bhartiya Chikitsa Avum Homeopathy Anusandhan Bhavan No. 61–65, opp. D Block, Janakpuri Institutional Area, Janakpuri, New Delhi- 110,058.

Telephone: 91-011-28525862/28,525,897/28,525,852.

Role of Study Sponsor & collaborator:

The funding agency has designed this study in consultation with the cardiologist & clinical pharmacologist at AIIMS New Delhi and will analyse the data and publish the results. The data management will be done by CCRAS's Central Biostatistical Monitoring Unit and the technical officers those are directly involved in this project.

Coordinating Centres:

- Central Ayurveda Research Institute, Road no 66, West Punjabi Bagh, Punjabi Bagh New Delhi, 110,026 which is a clinical unit of CCRAS at New Delhi.
- All India Institute of Medical Sciences, Ansari Nagar, New Delhi- 110,029, the study will be executed here.

Efficacy and safety of Ayurvedic Intervention (*Sarpgandha Mishran*) Vs Amlodipine for Stage-I Primary Hypertension- Study protocol for a Prospective Double-Dummy, Double-Blind, Placebo-Controlled Randomized Clinical Trial.

CTRI: CTRI/2021/12/038589, dated 13.12.2021.

Introduction

Background and rationale

Hypertension (HTN) is one of the most prevalent chronic non-communicable diseases with significant challenge associated with increased risk of cardiovascular diseases (CVDs) like coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation and peripheral artery disease, contributing to increased morbidity and mortality. It is estimated that 1.28 billion adults have HTN globally and only 21% have it under control [1]. India harbors 29.8% hypertension patients with significant difference between rural and urban parts [2].

The etiology of HTN involves interplay of multiple factors such as genetic predisposition, and environmental factors, including insulin resistance, high alcohol and salt intake, sedentary life style, stress and host factors like age, renal disease, certain medications, hypo/hyperthyroidism and coarctation of aorta. The maintenance of BP involves a complex mechanism that involves Renin-Angiotensin-Aldosterone system (RAAS), Sodium homeostasis regulation, natriuretic peptides, the endothelium, sympathetic nervous system, inflammation and the immune system.

The current treatment measures include use of various pharmacological agents such as ACE inhibitors, β blockers, calcium channel blockers, diuretics and α blockers. However, the use of these drugs has certain limitations

like side effects, use of multiple drug therapy, and inadequate success rate (34%) [3]. The introduction of adequate care right from the time of screening/detection, and attaining optimal control of Blood pressure is considered a public health challenge, considering that despite the availability of cost effective, safe and tolerated antihypertensive therapy, only < 14% of adults with hypertension have adequate BP control [1]. Hence, there is an urgent need to search for safe and effective therapeutic measures. The use of herbal medicines has been widely embraced over the past few decades and quality-assured Ayurvedic formulations has proven to have the potential to combat various diseases. Shafiq et al. in their study reported that 63.9% of their patients in a clinic in India took herbal medicine for hypertension [4]. Comprehensive scientific research must be conducted to establish a robust evidence base to scientifically substantiate the use of Ayurveda or traditional medicine as a viable option for HTN and to elucidate the extent to which Ayurveda contributes to achieving optimal blood pressure control and its role in addressing associated pathogenesis.

Sarpagandha Mishran is one of the most widely prescribed Ayurvedic intervention for the treatment of HTN. Sharma et al. in their case series reported that administration of M-*Sarpagandha Mishran* on patients of Stage 1 Primary HTN for 6 weeks was found to be safe and effective in significantly reducing the SBP and DBP by ~11% compared to the baseline [5]. Another retrospective analysis by Sharma et al. showed that Ayurveda medication (*Sarpagandha Mishran* and *Praval Pishti*) along with lifestyle management and yoga effectively controlled the blood pressure and helped in dose reduction/discontinuation of conventional medicines in EHTN patients [6]. Likewise, Kapoor et al. in their pilot study found that 8 weeks of therapy with *M-Sarpagandha Mishran* significantly reduced the SBP (126.6 ± 1.897), DBP (78.37 ± 1.264) and MBP (84.43 ± 1.268) in patients of Stage I and Stage II EHTN [7]. In another study it was observed that *Sarpagandha ghanvati* was safe and effective in improving the variables like SBP, DBP, MAP Hamilton anxiety rating scale, subjective sleep profiles and total cholesterol in patients with Primary HTN [8]. Although the safety and efficacy of *Sarpagandha Mishran* is already explored, there is a need to validate it scientifically in parlance with conventional treatment modality using a larger sample size.

Amlodipine is the first line and most preferred choice among the antihypertensive drugs used both in monotherapy and in combination. It effectively helps in lowering the blood pressure and improve patient outcomes owing to an array of factors such as neutral effect on comorbidities, ability to prevent activation of counter-regulatory mechanisms, anti-oxidant properties, enhanced NO production, cost effectiveness, good safety profile, once-daily dosage and long duration of action [9]. Therefore, this study aims to compare the safety and efficacy of *Sarpagandha Mishran* with the existing conventional treatment strategy for improving patient outcomes in HTN.

Objective(s)

The primary objective is to assess the clinical efficacy and the secondary objective is to assess the clinical safety of *Sarpgandha Mishran* in the Management of Stage-I Hypertension (JNC-VII report).

Trial Design

This investigation employs a Phase III, double-blind, randomized, double-dummy, placebo-controlled trial design, ensuring blinding for both participants and physicians. Enrolled participants will undergo a double-dummy placebo approach, receiving either Ayurveda intervention or contemporary medicine, with each participant assigned a corresponding placebo. The double-dummy design minimizes biases, controls for placebo effects, and maintains blinding, all of which contribute to the methodological strength of the study.

Methods: participants, interventions, and outcomes

Study setting

The study participants are being recruited from the Cardiology Outpatient Department at the All India Institute of Medical Sciences, New Delhi.

Eligibility criteria

Inclusion criteria

Participants of either sex aged 30–65 years, with Stage I hypertension, willing to participate and provide informed consent, fulfilling any of the criteria, *Viz.*, (1) Diagnosed patients of Stage-I essential hypertension as per 8th report of JNC (140–159 mm of Hg SBP and 90–99 mm of Hg DBP), (2) Individuals on Hydrochlorothiazide (HCT) up to 12.5 mg, and Blood Pressure (BP) in the range of 140–159 mm Hg SBP and 90–99 mmHg DBP or (3) Participants already on HCT (12.5 mg) and Amlodipine (> 5 &≤10 mg) and BP within the normal reference range will be included in the study.

Exclusion criteria

Individuals with secondary hypertension, a history of Acute Coronary Syndrome, Myocardial Infarction, congestive cardiac failure, stroke, or severe arrhythmia within the last 6 months will be excluded from the study. Additionally, those with uncontrolled Diabetes Mellitus (HbA1c > 8%) or taking oral hypoglycemics without

achieving glycemic control will not be eligible. Participants with concurrent hepatic dysfunction (AST and/or ALT > 3 times the upper normal limit), renal dysfunction (S. creatinine > 1.4 mg/dl), uncontrolled pulmonary dysfunction (asthmatic and COPD patients), or major systemic illnesses requiring long-term drug treatment (e.g., rheumatoid arthritis, neurological disorders, endocrinal disorders) or known cases of malignancy will also be excluded. Women planning for conception, pregnant, or lactating, individuals with psychosis/depressive illness and Hamilton's depression scale rating less than 7, a history of hypersensitivity to any trial drugs or their ingredients, participation in any other clinical trial, or the presence of conditions that, in the investigator's judgment, may jeopardize patient safety will also be considered exclusion criteria.

Patients visiting the Cardiology OPD with stage I HTN, on Amlodipine more than 5 mg and up to 10 mg would undergo a modified regimen with a combination of HCT (12.5 mg) and Amlodipine (5 mg) for a duration of 7 days, after obtaining informed consent. During this monitoring period, participants will be instructed to self-record their blood pressure twice daily and share the readings with the research team member through WhatsApp. In these 7 days of observation, if the participant has BP in the range of 140–159 mm of Hg SBP and 90–99 mm of Hg DBP), then, they will undergo screening. If eligible, they will be considered for enrollment in the study.

Interventions

Intervention for each group

The intervention period spans 12 weeks, during which patients will undergo systematic follow-ups for both efficacy and safety assessments. The participants in Group I-Ayurveda group (AG) will receive *Sarpagandha Mishran* [10] 500 mg capsule orally twice a day after food, and a placebo of Amlodipine 5 mg capsule (dummy) orally once a day after meal. Participants randomized to Group II will receive Amlodipine 5 mg capsules orally once daily along with matching placebo of *Sarpagandha Mishran* 500 mg capsules twice a day. Throughout the 12-week study duration, all participants, irrespective of their assigned groups, will receive Hydrochlorothiazide 12.5 mg tablets orally once daily to ensure that participants receive an established baseline treatment. The Ayurveda intervention and its matching placebo were sourced from Indian Medicines Pharmaceutical Corporation Limited (IMPCL); Amlodipine and its matching placebo were procured from Cipla and Hydrochlorothiazide was sourced from Sun Pharma laboratories limited, all GMP certified manufacturers. The placebos were meticulously designed to mirror the appearance of their respective active counterparts, ensuring identical packaging, color and shape. Figure 1 represents the scheduled study flow chart.

Criteria for discontinuing or modifying allocated interventions

The participants can be withdrawn from the trial at any time with no effect on their ongoing care in case of any major ailment necessitating the institution of new modalities of treatment or in case of non-compliance of the treatment regimen (minimum 80% compliance is essential to continue in the study) or when the blood pressure is not under control. The decision to withdraw a participant from the trial would be taken only by the Principal Investigator, who will then set out a detailed justification and also indicate the line of further management-if needed. The same would be informed to the Sponsor and the Institutional Ethics Committee within two working days.

Strategies to improve adherence to interventions

All participants were provided clear information about the study, its purpose, and the importance of adherence during the informed consent process. The participants would be educated on the potential benefits of adherence and the consequences of non- adherence. Medication adherence will be monitored during each follow-up visit and through weekly phone calls. The drug compliance will be assessed at each visit during the follow-up by counting the number of empty containers returned and assessing the approximate quantity of medicines consumed by the patient. Also, drug compliance report form will be provided to the study participants which has to be filled by the participant and submitted to the investigators during the follow-up visit.

Relevant concomitant care permitted or prohibited during the trial

Participants registered under the trial will be instructed to avoid the use of any other drugs on their own for any ailment and to consult the investigators for any symptom or complaint, or if they feel anything unusual. However, the participant can receive concomitant care as clinically required or any rescue medication in case of emergency as per the discretion of the Investigator and the same will have to be documented in the case record form.

Outcomes

The primary outcome assesses changes from baseline in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) at follow-ups on Days 15, 30, 60, and 90. Standard Measurement of Blood Pressure for the assessments at each follow-up:

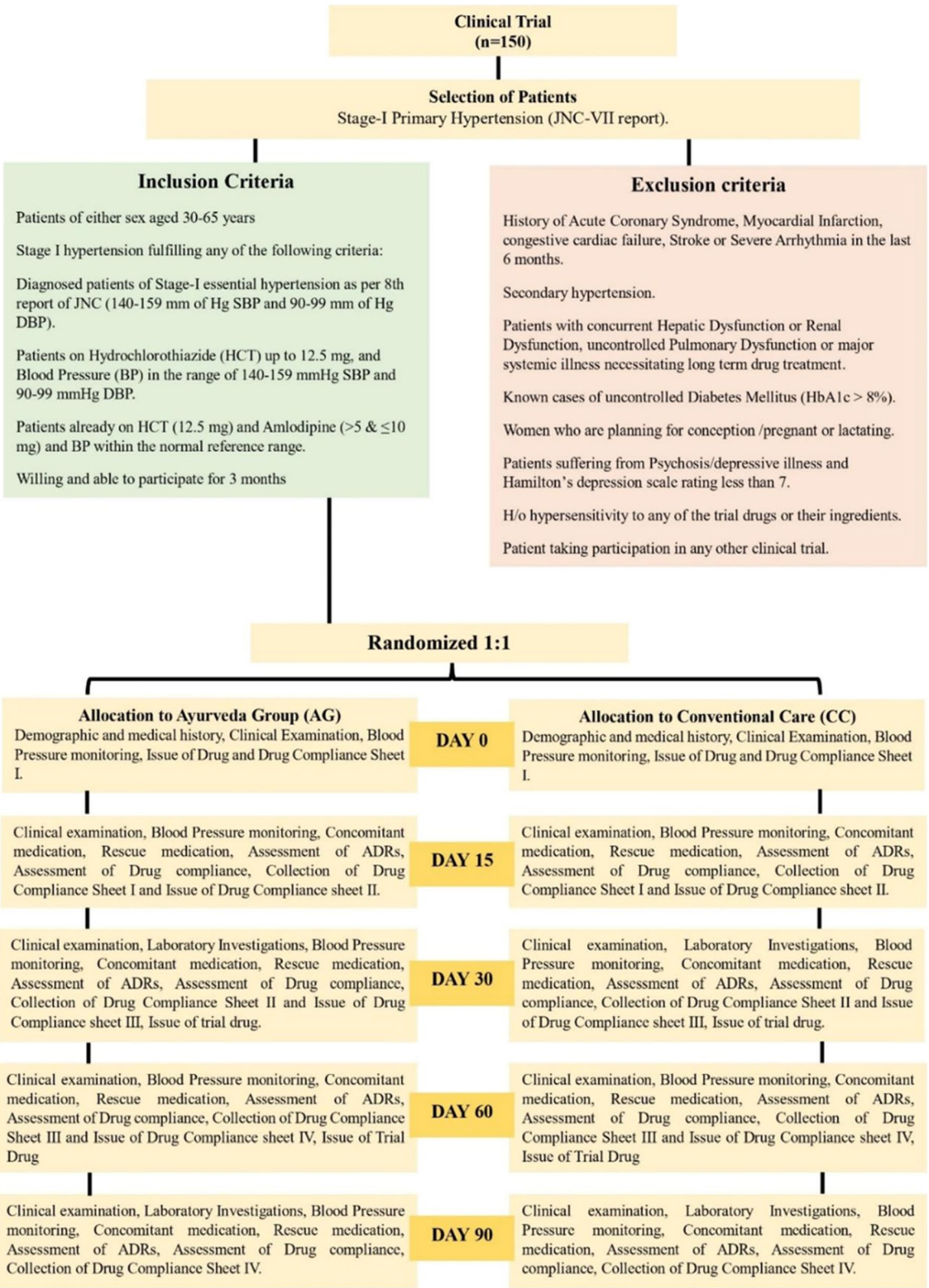

Fig. 1 The Flowchart depicting the schedule of the trial

Blood pressure (BP) will be measured using a standardized bladder cuff (12–13 cm wide and 35 cm long). Participants will be seated comfortably in a quiet environment for 5 min before BP measurements commence. The cuff will be positioned at heart level, with back and arm support to prevent muscle contraction and exercise-induced BP increases. During the initial visit, BP will be measured in both arms to identify any between-arm differences. The arm with the higher value will be used as the reference. Three BP measurements will be taken, 1–2 min apart, and additional measurements will be conducted only if the first two readings differ by more than 10 mmHg. The recorded BP will be the average of the last two readings.

Secondary Outcome Measures: The secondary outcome measures include assessment of change in laboratory of inflammatory markers such as IL-6, Serum Pro-BNP, oxidative stress parameters Glutathione peroxidase, Catalase and Superoxide dismutase and also lipid profile, at Day 90 compared with baseline. The impact of trial interventions on the participants' quality of life will be examined through the change in SF-36 Health Survey Score on Day 90 in comparison to baseline. Secondary outcomes also include the assessment of safety by recording any adverse events (AE) or adverse drug reactions (ADR) reported by study participants. And also, through changes in liver function tests (LFT) and renal function tests (RFT) parameters in study participants from baseline.

Adverse events will be documented at each visit, and their seriousness, severity, relationship to the study medication, duration, frequency, outcome, and required therapeutic measures will be carefully assessed and recorded. All SAE/ADR would be reported to the Sponsor and the IEC.

Participant timeline

The participant timeline is presented in Fig. 2.

Sample size

The sample size for this clinical study was determined based on the evidence from a previous study [11] on Amlodipine- 5 mg for stage I hypertension wherein a mean difference of 15 mm Hg in systolic blood pressure (SBP) was reported after treatment. It was assumed, based on clinical experience, that Ayurveda intervention might produce a difference of 20 mm Hg at the end of treatment. Considering a standard deviation of 10 mm Hg, a statistical power of 80%, and a significance level of 0.05, the sample size was calculated as 126. Taking into account, an attrition rate of 20% and rounding up to ensure that we have enough statistical power to detect meaningful differences in blood pressure between the Ayurveda intervention and the standard treatment, a total sample size of 150 was calculated for the study.

Recruitment

The participants with HTN attending the Cardiology OPD of All India Institute of Medical Sciences, New Delhi, who provided informed consent for participation after providing the Participant Information Sheet (PIS), will be screened based on the selection criteria and those eligible were recruited for participation and issued a participant enrollment ID.

Methods: assignment of interventions

Randomization and allocation

In the double-blind, double-dummy placebo-controlled trial, participants will undergo randomization in a 1:1 ratio to either the Ayurveda Group or the conventional care group. The randomization process will be executed using a computer-generated, block randomization schedule created by an independent statistician.

To maintain allocation concealment in this double-dummy design, each set of interventions and their corresponding placebos will be packaged in identical wrapping and labeled with sequential enrollment numbers, as dictated by the randomization list. This packaging process will be carried out by an independent team comprising statisticians and representatives from the drug cell of the sponsor. Throughout the entire trial duration, including enrollment and subsequent follow-ups, all participants, care providers, and investigators will be unaware of the trial-group assignment. Blinding will be rigorously maintained to ensure unbiased outcomes.

In the event of an emergency situation necessitating unblinding, a systematic protocol has been established. Should the need arise for unblinding, the sealed code break envelopes, each corresponding to a unique participant enrolment ID, issued by the Sponsor and securely stored under the supervision of the principal investigator, will be opened in accordance with the predetermined guidelines with due intimation to the sponsor, ensuring transparency and adherence to ethical standards.

Data collection methods

Plans for assessment and collection of outcomes

After informing the participants about the research study as per Patient Information Sheet, written consent (in triplicate) will be taken from the participants before screening them. After screening the participants, the eligible participants will be included in the study and data will be collected in a case record form. The data will be subsequently recorded in an e-format for statistical analysis and record.

Procedures	Screening	Baseline	15th Day	30th Day	60th Day	90th Day
Informed consent	✓					
Demographic & Medical History		✓				
CBC	✓			✓		✓
ESR	✓			✓		✓
Fasting Blood Sugar	✓			✓		✓
HbA1c	✓					✓
LFT	✓			✓		✓
KFT	✓			✓		✓
Lipid Profile	✓			✓		✓
Sr. TSH	✓					
IL6	✓					✓
Sr. Pro BNP	✓					✓
Superoxide dismutase (SOD)	✓					✓
Catalase (CAT)	✓					✓
Glutathione peroxidase (GPX)	✓					✓
ECG	✓					✓
Chest X-ray	✓					
Blood Pressure		✓	✓	✓	✓	✓
Clinical examination		✓	✓	✓	✓	✓
Concomitant Medication			✓	✓	✓	✓
Rescue Medication			✓	✓	✓	✓
Assessment of ADRs			✓	✓	✓	✓
Issue of Drug Compliance Sheet		✓	✓	✓	✓	
Assessment of drug compliance			✓	✓	✓	✓
Issue of Trial drug		✓		✓	✓	

Fig. 2 Timeline of the study

Data collection and management

Information pertaining to participant demographics, clinical assessments, laboratory investigations, and Quality of Life metrics will be meticulously recorded in structured Case Report Forms (CRFs) and electronic-CRFs (e-CRFs) during screening, baseline, and subsequent follow-up visits. Participants will be identified solely by their unique participant codes, ensuring confidentiality by avoiding the use of participant names. The completed CRFs will be securely stored in designated cabinets, accessible only to the Principal Investigator and/or designated team members. Additionally, e-CRFs will be safeguarded on password-protected laptops to prevent unauthorized access. Data entry into the CRFs will undergo a rigorous validation process overseen by the Principal Investigator. This involves thorough checks to ensure data completeness and accuracy, addressing any inconsistencies or missing information.

Statistical methods

Reporting will adhere to CONSORT guidelines, and data analysis will be conducted following the principle of intention to treat (ITT). Additionally, per-protocol analysis will be performed for outcome variables. The

presentation of data will include mean ± standard deviation for quantitative variables and number/percentage for categorical variables.

The Statistical Package for Social Sciences (SPSS) version 26.0 will be employed for data analysis. For normally distributed quantitative data, independent-samples t-test or one-way analysis of variance (ANOVA) will be utilized. The paired-sample t-test will assess the effects within each group before and after treatment.

Qualitative data will undergo analysis using Chi-square (Fisher's exact test or Monte Carlo exact test) or nonparametric techniques, specifically the Kruskal-Walli's test. All statistical tests will be two-tailed, and a significance level of 0.05 will be applied. Adverse Events and Serious Adverse Events will be summarized descriptively for each group.

Data monitoring

A Data Monitoring Committee has been constituted, comprising 1 Ayurveda expert, 1 independent biostatistician, 1 subject expert, and 2 independent expert members with specialization in clinical trials. This committee is tasked with the systematic and periodic review of trial data, aiming to provide informed recommendations regarding the trial's continuation, modification, or termination, as necessary, safeguard the interests of the participants, monitor and evaluate adverse events, and ensure the overall integrity and ethical conduct of the trial. Interim Analysis: An interim analysis will be conducted in accordance with the recommendations of the Data Safety Monitoring Board (DSMB) under specific circumstances that necessitate a comprehensive review of study safety and protocol adherence. Instances triggering an interim analysis include a notable increase in the occurrence of Serious Adverse Events (SAE) or Adverse Drug Reactions (ADR) that warrants a reassessment of the safety profile of the study interventions. Additionally, if a considerable number of participants require withdrawal from the trial or the administration of rescue medication, or if participant dropouts are notably attributed to tolerability issues, an interim analysis will be initiated to take a decision regarding trial continuation or termination.

Harms

Any adverse event identified during the treatment period or follow-up visits will be meticulously documented, and it's appropriate and timely management will be executed. The Principal Investigator will promptly communicate such adverse events to the Ethics Committee and the sponsor in a structured format, ensuring the comprehensive reporting of pertinent information.

Auditing

The study will undergo regular monitoring by the Central Biostatistics and Monitoring Unit of the Sponsor. The oversight of the trial will be conducted by project monitors through routine site visits, supplemented by scheduled quarterly virtual monitoring sessions. Periodic on-site inspections will involve a thorough examination of source documents, data records, and regulatory compliance and also include scrutinizing the informed consent process, ensuring participant confidentiality, and assess whether the adverse event reporting is appropriately done.

Research Ethics approval

The study protocol has been approved by the institutional Ethics committees of All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India on 13th August 2019 (vide IEC-311/03.05.2019, RP-39/2019, RP-06/2019) respectively. The study will be conducted in accordance with the principles of Declaration of Helsinki and the ICMR's National Ethical Guidelines for Biomedical and Health Research on Human Participants (2017).

Protocol amendments

The trial will be conducted in compliance with the protocol. Deviations from the protocol will not be made except when necessary to alleviate an immediate hazard to trial patients. All the protocol amendments, including changes to interventions, examination, data collection and method of analysis will be reported to the sponsors and IEC at the earliest along with the exact reason.

Consent

Written informed consent will be taken from all the eligible and willing participants before their screening by the investigators or the approved health professional.

Confidentiality

All study-related information shall be stored securely at the study site. All the data collected in case record forms will be entered in an e-format developed by the CCRAS headquarters. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to

other identifying information will be stored in a separate, locked file in an area with limited access.

Conflict of interest

The study is designed and conducted with an unwavering commitment to scientific rigor, patient welfare, and the advancement of scientific knowledge and the investigators involved in this clinical trial declare that there are no competing interests.

Access to data

Raw data generated at study center will be processed to the derived data supporting the findings of this study at the Central Council for Research in Ayurvedic Sciences (Sponsor).

Ancillary and post-trial care

Upon the conclusion of the study period, participants will receive ancillary and post-trial care as needed.

Dissemination policy

The outcomes of this study will be disseminated through the publication of research findings in peer-reviewed scientific journals and presentations at relevant scientific conferences and forums may be considered.

Discussion

Hypertension and comorbid cardiovascular diseases (CVD) pose a significant global burden, with the prevalence increasing every year. As such, it is crucial to develop effective clinical trial protocols to assess novel interventions and treatment strategies. Recent clinical trials have focused on exploring combination therapies, evaluating new techniques, and considering special populations to address better adherence and control of blood pressure within age-appropriate reference ranges. Some studies have suggested that more intensive blood pressure reduction can provide substantial health benefits that outweigh the risks of adverse events [12].

Despite advancements in the management of hypertension, the overall control of blood pressure in the general population remains unsatisfactory. Studies have shown that only a small percentage (approximately 15–20%) of hypertensive individuals achieve the recommended blood pressure values set by guidelines [13]. The failure to achieve adequate blood pressure control is considered a major factor contributing to hypertension-related mortality worldwide [14].

The hypertensive treatment guidelines in the last decades have emphasized the use of combination therapies involving two or more antihypertensive drugs, which not only leads to a more rapid reduction in blood pressure but also reduces the heterogeneity of the blood pressure response between patients. Additionally, it has been reported that combination therapy facilitates up titration of treatment, resulting in improved outcomes [15].

Furthermore, evidence suggests that initial combination therapy can effectively overcome therapeutic inertia, which has been proposed as a common barrier to effective hypertension management [16]. Considering these advancements and the persistently high prevalence of uncontrolled hypertension, it is prudent to explore alternative therapeutic options. This clinical trial protocol aims to investigate the therapeutic potential of *Sarpagandha Mishran*, an Ayurveda intervention, in conjunction with the contemporary care regimen of Hydrochlorothiazide (HCT) 12.5 mg in comparison with conventional care of HCT-12.5 mg and Amlodipine-5 mg in Stage I hypertension, with the goal of optimizing blood pressure for individuals with hypertension in India. Given the global burden of hypertension and the observed suboptimal control with conventional treatments, exploring alternative interventions becomes imperative.

This clinical trial stands as a pioneering effort, representing the first adequately powered comparison of an integrative treatment protocol featuring an Ayurveda component as an adjunct to conventional care, against a combination therapy utilizing two conventional care antihypertensives. The uniqueness of this trial lies in its focus on integrative strategies, acknowledging the complementary potential of Ayurveda alongside conventional care. The outcomes are anticipated to go beyond the immediate scope of the study, offering valuable insights into novel approaches for hypertension treatment in India. Ultimately, the significance of this research extends to its potential to influence clinical practices and guide healthcare policies, fostering a more comprehensive approach to blood pressure regulation.

Acknowledgements

The authors express gratitude for the cooperation of the former Director General, CCRAS, Prof. Vaidya K. S. Dhiman, whose support played a pivotal role in the initiation of this study. Special recognition is also extended to the biostatistics team at CCRAS headquarters for their valuable assistance in sample size estimation.

Author contributions

B.Y. developed the protocol and reviewed the article. BCSR conceptualized the idea and developed the protocol in consultation with the investigators and approved the final version. The overall co-ordination of the study is dealt by them. DSA vetted the study design and conducted the study under his supervision as Investigator. RN gave his expertise in designing, revision and finalization of the protocol. SJ edited and reviewed the protocol and drafted the protocol article in consultation with the investigators and study coordinators. SK actively involved in the conceptualization and finalization of the study interventions and reviewed the article. SS coordinated the study as a co-investigator and reviewed the protocol and article. DD prepared the zero draft of the protocol article and reviewed the literature. AS reviewed the literature and delt with the initial technical issues related to ethical clearance. RS gave methodological inputs and is involved in handling the statistical part of the protocol including sample size calculation, randomization and plan of analysis. RB worked as Senior Research Fellow for 5 months delt with the technical

issues related to the protocol finalization and provided logistical support. BG over all coordinated the project and provided scientific insights. and mentorship NS provided the overall guidance in conceptualization, finalization of protocol, methodological inputs and article review as the technical team head.

Funding
Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Government of India, New Delhi.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol has been approved by the institutional Ethics committees of All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India on 13th August 2019 (vide IEC-311/03.05.2019, RP-39/2019, RP-06/2019) respectively.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.After informing the participants about the research study as per Patient Information Sheet, written consent (in triplicate) will be taken from the participants before screening them.

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Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Government of India, New Delhi.

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