Transcutaneous electrical acupoint stimulation for high-normal blood pressure: study protocol for a randomized controlled pilot trial

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Study protocol

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Abstract

Background: High-normal blood pressure (BP) is associated with increased all-cause, cardiovascular mortality and frequently progresses to hypertension. Transcutaneous electrical acupoint stimulation (TEAS) might be a non-pharmaceutical therapy option to control BP. This trial aims to determine the efficacy and safety of TEAS combined with lifestyle modification for high-normal BP.

Methods/design: This prospective, randomized and parallel clinical trial will be conducted in a community service center in China. Sixty participants with high-normal BP will be randomly allocated to receive TEAS plus lifestyle modification (intervention group) or lifestyle modification alone (control group) in a 1:1 ratio. In addition to lifestyle modification, the intervention group will receive TEAS at four acupoints for 30 minutes, 4 times weekly for 12 weeks for a total of 48 sessions at home. The control group will receive same lifestyle modification but no TEAS. The primary outcome will be the change in mean systolic blood pressure at 12-week from the baseline measurement. Secondary outcomes include the change of mean diastolic blood pressure, proportion of subjects with progression to hypertension, quality of life, physical activity, body mass index and waist circumference. Adverse events during the trial will be monitored.

Discussion: This trial will explore the feasibility and provide potential evidence for the efficacy and safety of TEAS plus lifestyle modification for high-normal BP. The results of this study will be published in a peer-reviewed journal.

Trial registration: Chinese Clinical Trial Registry, ChiCTR1900024982. Registered on August 6, 2019.

Background

Increased blood pressure (BP) is a leading modifiable risk factor for global disease burden and premature mortality [1, 2], even mild BP elevations manifesting as ‘prehypertension or high-normal BP’ have been associated with increased all-cause mortality [3]. High-normal BP elevates the risk of higher morbidity and mortality from cardiovascular disease (CVD) and stroke [4, 5], as well as increasing the risk of incident end-stage renal disease [6]. High-normal BP frequently progresses to hypertension [7], and affects approximately 41.3% (estimated 435.3 million) of adults in China according to the Chinese guideline [8]. High-normal BP may be a window of opportunity to prevent hypertension and its cardiovascular consequences [9]. The 2018 Chinese Guidelines for Prevention and Treatment of Hypertension defined high-normal BP as systolic blood pressure (SDP) of 120–139 mmHg and/or diastolic blood pressure (DBP) of 80–89 mmHg [10]. However, the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) BP guideline defined stage 1 hypertension as SBP of 130–139 mmHg or DBP of 80–89 mmHg [11]. Therefore, a large number of individuals who had prehypertension or high-normal BP before are now considered to have hypertension according to the new American guideline.

Data are lacking as to how this range of BP should be managed and most guidelines do not recommend pharmacological interventions for high-normal BP without cardiovascular comorbidity [7]. Long-term medication is costly to control BP particularly in developing nations, for instance, the price in China was 3.3 times the price in the United States on average [12]. Despite limited effectiveness, virtually all guideline statements recommend and encourage lifestyle interventions to prevent hypertension [7]. However, lifestyle modification is a dynamic process and requires long-term persistence [13], and the challenges of life-style changes extend beyond counseling for physicians and patient adherence [14]. For the majority of US adults with a SBP of 130–139 or DBP of 80–89 mm Hg, non-pharmaceutical therapy by itself is the recommended treatment [15].

Acupuncture as a non-pharmaceutical therapy is widely used in the treatment of hypertension [16], and some evidence suggests potential effectiveness [17]. Transcutaneous electric acupoint stimulation (TEAS), a noninvasiveness therapy similar to acupuncture, is used as a clinical alternative to electrical acupuncture and manual acupuncture [18]. TEAS has the advantages of being easy to use, which is more “user friendly” requiring minimal training for physicians and patients, and if convenient for clinical application [19]. Previous studies have shown that TEAS has effects on the nervous system, that include regulation autonomic nervous system function and enhancement of the activity of the vagus nerve, thereby potentially affecting BP [20]. However, studies of TEAS for high-normal BP are lacking. The main objective of this preliminary trial is to assess the efficacy and safety of TEAS combined with lifestyle modification in participants with high-normal BP, to calculate the sample size for a future efficacy study.

Methods

Study design

This prospective, randomized and parallel design clinical trial of high normal BP participants will be conducted in a large public-sector clinic in Beijing, China. The trial protocol was approved and reviewed by the Ethics Committee of Beijing University of Chinese Medicine, and will be reported based on SPIRIT guidelines. The corresponding author will be responsible for trial scientific oversight. The study was registered on Chinese Clinical Trial Registry (ChiCTR1900024982) on August 6, 2019.

Study population

The study population will be comprise of individuals with high-normal BP (2018 Chinese Guidelines for Prevention and Treatment of Hypertension [10]) at a community service center (Nanyuan community health service centers in Beijing, China). All participants will provide written informed consent before enrollment.

Inclusion criteria

1. Aged between 35 and 65 years (either sex)
2. SBP of 120-140 mmHg and/or DBP of 80-90 mmHg on at least 2 separate visits

3. No language disorder or mental retardation, so that participants will be able to answer and complete the questionnaire completely
4. Willing to sign written informed consent

Exclusion criteria

1. Contraindications for the use of electrostimulation: such as use of a cardiac pacemaker or other implanted medical devices; suffering from acute diseases, infectious diseases, malignant tumors, cardiovascular disease, cerebrovascular disease, liver and kidney dysfunction or other malignant diseases; dermatological abnormalities on the skin of the acupuncture points
2. Secondary hypertension
3. Received antihypertensive drugs or other drugs that affect BP in the previous 2 months
4. Uncontrolled diabetes
5. Received acupuncture treatment in the previous 1 month
6. Drug or alcohol abuse
7. Pregnant, lactating or planning pregnancy during the trial
8. Participated in another research trial

Randomization and allocation concealment

Eligible participants will be randomized into one of two groups: the intervention group, or the control group (1:1), using block random method and the block size is 6. The randomization sequence will be prepared by a professional statistician (Na Zhang) with the SAS9.3 software, who is not involved in assessment, treatment or analysis of the study, to ensure balance in baseline BP across the groups. When an eligible participant needed to receive a random group, the random number and the group assignment will be sent from the random number administrator to the recruiter via phone or short message.

The participants and study staff interacting with participants will not be blinded to group assignment in the trial. The outcome assessors and trial statisticians, who will not be involved in the intervention, will be blinded.

Interventions

Transcutaneous electrical stimulation will be applied to the acupuncture points in the intervention group, and the control group will not have TEAS. Both groups will be educated about lifestyle modification.

TEAS

A household transcutaneous nerve stimulator (SDP-330; Yuwell, Suzhou Medical Appliances Co, Ltd., Suzhou, China) with two 100-Hz output channels at a pulse width of 0-100 μs will be used for the application of TEAS. It has 10 different stimulus intensities, and the intensity of the stimulation will be individually adjusted by the participants with the recommendation to increase the intensity gradually to

trigger the maximum sensory threshold without discomfort or pain. The self-adhesive electrodes measuring 5 × 5 cm will be placed on the acupuncture points region. The stimulator has 8 different modes, but the participants will be asked to select one of the “press” or “knock” or “knead” mode, which cannot be changed during treatment. The participants will be asked to keep a treatment diary and register the time of stimulation.

The following four bilaterally acupoints with relevance for BP lowering according to traditional Chinese medicine concepts determined by a literature review [21] will be used in the intervention group: *Hegu* (LI4), *Quchi* (LI11), *Zusanli* (ST36), and *Taichong* (LR3) (Table 1 and Figure 1). The first treatment will be at LI4 and LI11 on the same arm for 15 minutes, followed by the same acupoints on the opposite arm for 15 minutes. The second treatment will be at ST36 and LR3 on the same leg for 15 minutes, and then the same acupoints on the opposite leg will be took for 15 minutes. Each treatment will last a total of 30 minutes, and different acupoints will be used. Participants will be asked to alternate treatment on alternate days to guarantee they will receive 4 times TEAS per week and 48 times in total, and cannot increase or decrease the number of times.

Each participant in the intervention group will receive a stimulator with written instructions as well as the participants’ manual on how to do the TEAS treatment properly. Treatment will be performed at the participants' home, and TEAS will be performed by the participants. At the beginning of the trial, the study investigators will instruct the participants to locate the acupoints. Participants will be asked to take photos to provide feedback to investigators during the initial treatment, to ensure that participants can accurately find all 4 acupoints. In addition, acupoint pictures and videos will be produced to assist participants. Study investigators will ensure the participants fully understand the operation of TEAS and the location of acupoints. Figure 2 shows the study design.

Lifestyle modification

Participants in both groups will receive recommendation for lifestyle modification. All participants will receive relevant weekly information through the WeChat app (Tencent, Shenzhen, China) in mobile phone and monthly educational activities in the community. They contain information about weight control, increase physical activity, healthy eating, dietary sodium reduction, smoke abatement and set limit to alcohol.

Outcomes

Primary outcome

The primary outcome will be the change in mean SBP from baseline to 12 weeks.

BP will be measured as proposed by the 2018 Chinese Guidelines for Prevention and Treatment of Hypertension [10]. Participants will be asked to avoid exercise, alcohol, cigarettes and coffee/tea for at least 30 minutes before the BP measurement. BP will be measured with the participant in a seated position after 5 minutes of quiet rest. A digital BP monitor (HEM-7136, OMRON Corporation, Kyoto,

Japan) with suitable cuff size will be used. Clinicians will record three sequential BP readings at 5-minute intervals, and the final BP will be calculated by removing the initial reading and calculating the mean from the two remaining readings.

Secondary Outcomes

Changes in mean blood pressure at other time points

Other secondary outcomes include measures of changes in mean SDP and DBP from baseline to 4, 8, 12, 24 and 36 weeks.

Proportion of progression to hypertension

The proportion of subjects with hypertension (BP>140/90 mmHg) will be calculated among the high-normal BP participants at 12, 24 and 36 weeks.

Quality of life (QoL)

The 12-item Short Form Health Survey (SF-12) [22] will be used for quality of life at baseline, 12, 24 and 36 weeks. The questionnaire consists of a mental domain and a physical domain (each domain ranges from 0 to 100), and a higher score will be considered to indicate a better quality of life.

Physical activity

Change in physical activity will be assessed by use of the Chinese version of the International Physical Activity Questionnaire (IPAQ) [23, 24] at baseline, 12, 24 and 36 weeks.

Body mass index (BMI) and waist circumference

Net change in BMI and waist circumference will be measured at baseline, 12, 24 and 36 weeks. The BMI, defined as the weight (kg) divided by the participant's height squared (m^2) [25], will be calculated as an index for obesity. And the waist circumference will be measured (at the smallest circumference between the iliac crest and the lower costal margin) in centimeters (cm).

Adverse events (AEs)

Any AEs will be monitored and documented throughout the trial by the investigators and participants. Based on their potential association with the TEAS procedure, AEs will be categorized by specialists as treatment-related or non-treatment-related within 24 hours of occurrence. Potential AEs of TEAS used in the trial include continuous post-electrostimulation sensation, and skin numbness. The schedule of enrolment, intervention and assessments is shown in Figure. 3.

Quality Assurance and Quality Control

To guarantee the quality of the study, the trial protocol was reviewed and revised by experts in hypertension, acupuncture, methodology and statistics. A pre-specified standard operating procedure of BP measurement, including selection of appropriate cuffs, reading and calculation of mean BP, maintain and calibrate of electronic sphygmomanometer will be developed to reduce measurement error. Other standardized procedures for the operational aspects of the study include details in filling out questionnaires, recruitment, lifestyle intervention coaching, assessment of AEs and data management will also be used to train the study personnel. The Clinical Research Associate (CRA) will review the data regularly, for authenticity and timeliness of data collection, and data quality. All data will be collected onto paper questionnaires and then transferred to an Excel spreadsheet, and will be preserved for at least five years after publication of the trial results. Detailed instructions, acupoint pictures, videos and treatment procedures of the TEAS will be produced and distributed to each participant in the intervention group. Study investigators will ensure participants' compliance with the intervention protocol. Participants will be registered with a phone number and address for further contact in case of missing outlined visits.

Statistical methods

Sample size

This pilot study aims to assess the efficacy and safety of TEAS combined with lifestyle modification for high-normal BP, and determine the feasibility of a further large clinical trial. The minimum sample size for exploratory trials is 20 to 30 per group according to Provisions for Drug Registration in China. We selected the maximum of 30 participants, and the sample size of 60 participants was determined. The results of this study will facilitate the calculation of an appropriate sample size for further randomized clinical trials.

Statistical analysis

Analysis will be carried out on an intention-to-treat (ITT) basis and will be performed using SPSS 23.0 statistical software (IBM SPSS Statistics, New York, USA) with a 2-sided *P* value of less than 0.05 considered significant. The measurement of data that conforms to the normal distribution will be expressed as mean ± SD, and the measurement data that does not conform to a normal distribution will be expressed by the median (interquartile range), and counting data will be represented by cases (percentages). The continuous variables will be evaluated by using a *t* test or the Mann-Whitney U test for comparison. The Chi-square test or Fisher’s exact test will be employed to compare binary variables. Missing data will be imputed using the last observation carried forward.

Discussion

This manuscript presents the design of a randomized controlled pilot trial testing the efficacy and safety of TEAS combined with lifestyle modification to improve BP control. We are not aware of any previously

published studies that have reported the efficacy of TEAS combined with lifestyle modification in participants with high-normal BP.

Numerous studies have confirmed that high-normal BP is highly prevalent and increases the risk of incident hypertension, cardiovascular events and death[7]. In China and other low-income and middle-income countries, long-term medication is costly to control BP. The intervention for the trial is innovative. For individuals with high-normal BP, exploring non-pharmaceutical therapies is feasible and necessary. Domestic TEAS may be an appropriate form of intervention. TEAS will perform by participants themselves at home, reducing transportation costs and possibly increasing compliance. Study investigators will ensure the participants fully understand the operation of TEAS. The education of lifestyle modification based on a commonly used social media software is also low-cost. Therefore, the intervention model characterized by accessibility, flexible and low cost.

A limitation in the present study is the failure to clarify the optimal frequency of electrical stimulation of TEAS. Second, the participants are not blinded to the nature of intervention. At the end of this pilot trial, the results will potentially provide evidence of the feasibility and efficacy of TEAS combined with lifestyle modification for high-normal BP and, if effective, a future large clinical will be conducted.

Trial Status

Protocol: version 2.0, 30 June 2019

Date opened to recruitment: 6 September 2019

Expected recruitment closure: 1 April 2020

Abbreviations

TEAS: transcutaneous electrical acupoint stimulation; BP: blood pressure; CVD: cardiovascular disease; SDP: systolic blood pressure; DBP: diastolic blood pressure; SF-12: 12-item Short Form Health Survey; IPAQ: International Physical Activity Questionnaire; BMI: Body mass index; AEs: Adverse events; CRA: Clinical Research Associate; ITT: intention-to-treat

Declarations

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Availability of data and materials

Not applicable as this is a study protocol and does not contain data or results.

Authors' contributions

CZ Liu, YW, LQ Wang and Y Wang studied the concept and designed the manuscript; YW drafted the manuscript; LQ Wang critically revised the manuscript for important intellectual content; JW Yang and JH Liu drew up the statistical analysis plan; LQ Wang obtained funding; JF Tu, GX Shi and ZX Tian involved in administrative, technical, or material support; and YS Qi supervised the study. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Ethics approval and Consent

The trial protocol was approved and reviewed by the Ethics Committee of Beijing University of Chinese Medicine (2019BZHYLL0208). Participants provided written informed consent prior to randomization.

Consent for publication

Not Applicable.

Competing interests

The authors have no conflict of interest. Suzhou Medical Appliances Co, Ltd. and OMRON Corporation had no role in the conduct of the study.

References

1. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ, Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. Lancet. 2002;360:1347-60.
2. He J, Gu D, Wu X, Reynolds K, Duan X, Yao C, et al. Major causes of death among men and women in China. N Engl J Med. 2005;353:1124-34.
3. He J, Gu D, Chen J, Wu X, Kelly TN, Huang JF, et al. Premature deaths attributable to blood pressure in China: a prospective cohort study. Lancet. 2009;374:1765-72.
4. Huang Y, Wang S, Cai X, Mai W, Hu Y, Tang H, et al. Prehypertension and incidence of cardiovascular disease: a meta-analysis. BMC Med. 2013;11:177.

5. Huang Y, Cai X, Li Y, Su L, Mai W, Wang S, et al. Prehypertension and the risk of stroke: a meta-analysis. Neurology. 2014;82:1153-61.
6. Huang Y, Cai X, Zhang J, Mai W, Wang S, Hu Y, et al. Prehypertension and Incidence of ESRD: a systematic review and meta-analysis. Am J Kidney Dis. 2014;63:76-83.
7. Egan BM, Stevens-Fabry S. Prehypertension--prevalence, health risks, and management strategies. Nat Rev Cardiol. 2015;12:289-300.
8. Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, et al. Status of Hypertension in China: Results From the China Hypertension Survey, 2012-2015. Circulation. 2018;137:2344-56.
9. Fuchs FD, de Mello RB, Fuchs SC. Preventing the progression of prehypertension to hypertension: role of antihypertensives. Curr Hypertens Rep. 2015;17:505.
10. Joint Committee for Guideline Revision. 2018 Chinese Guidelines for Prevention and Treatment of Hypertension-A report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. J Geriatr Cardiol. 2019;16:182-241.
11. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:1269-324.
12. Bai G, Bennet C, Wang J, Anderson GF. Access to Antihypertensive Drugs in China. Circulation. 2018;138:1777-9.
13. Mahmood S, Shah KU, Khan TM, Nawaz S, Rashid H, Baqar S, et al. Non-pharmacological management of hypertension: in the light of current research. Ir J Med Sci. 2019;188:437-52.
14. Janke EA, Richardson C, Schneider KL, Society of Behavioral Medicine Executive Committee. Beyond Pharmacotherapy: Lifestyle Counseling Guidance Needed for Hypertension. Ann Intern Med. 2019;170:195-6.
15. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, et al. Potential US Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. Circulation. 2018;137:109-18.
16. Zhao H, Li D, Li Y, Yang Y, Liu Y, Li J, et al. Efficacy and safety of acupuncture for hypertension: An overview of systematic reviews. Complement Ther Clin Pract. 2019;34:185-94.
17. Wang J, Xiong X, Liu W. Acupuncture for essential hypertension. Int J Cardiol. 2013;169:317-26.
18. Li H, Wu C, Yan C, Zhao S, Yang S, Liu P, et al. Cardioprotective effect of transcutaneous electrical acupuncture point stimulation on perioperative elderly patients with coronary heart disease: a prospective, randomized, controlled clinical trial. Clin Interv Aging. 2019;14:1607-14.
19. Chen WT, Wei JF, Wang L, Zhang DW, Tang W, Wang J, et al. Effects of perioperative transcutaneous electrical acupoint stimulation on monocytic HLA-DR expression in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass: study protocol for a double-blind randomized controlled trial. Trials. 2019;20:789.

20. Shi L, Fang J, Zhao J, Liu G, Zhao Q, Zhang J, et al. Comparison of the Therapeutic Effects of Acupuncture at PC6 and ST36 for Chronic Myocardial Ischemia. Evid Based Complement Alternat Med. 2017;2017:7358059.
21. Liu H, Wang Y, Gao H, Chen Y, Yang J, Aiping L. Literature Research on Acupuncture Point Selection for Hypertension. J Tradit Chin Med. 2014;55:1055-8.
22. Wan E, Yu E, Chin WY, Choi E, Wu T, Lam C. Evaluation of the responsiveness of Short Form-12 Health Survey version 2 (SF-12v2) in Chinese patients with hypertension in primary care. Qual Life Res. 2019;28:2851-7.
23. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35:1381-95.
24. Qu NN, Li KJ. [Study on the reliability and validity of international physical activity questionnaire (Chinese Vision, IPAQ)]. Zhonghua Liu Xing Bing Xue Za Zhi. 2004;25:265-8.
25. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363:157-63.

Figures

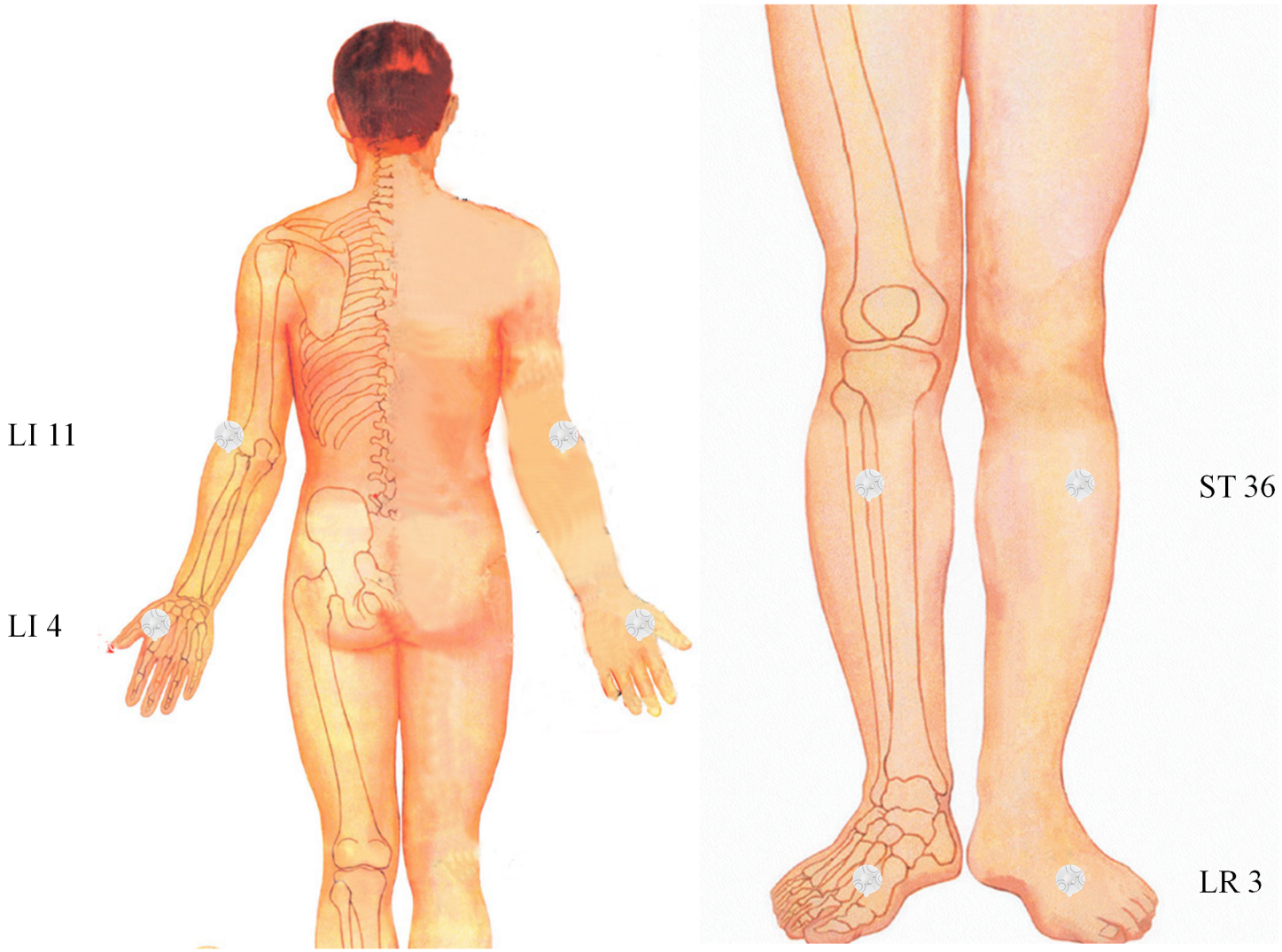

Figure 1

Locations of acupoints.

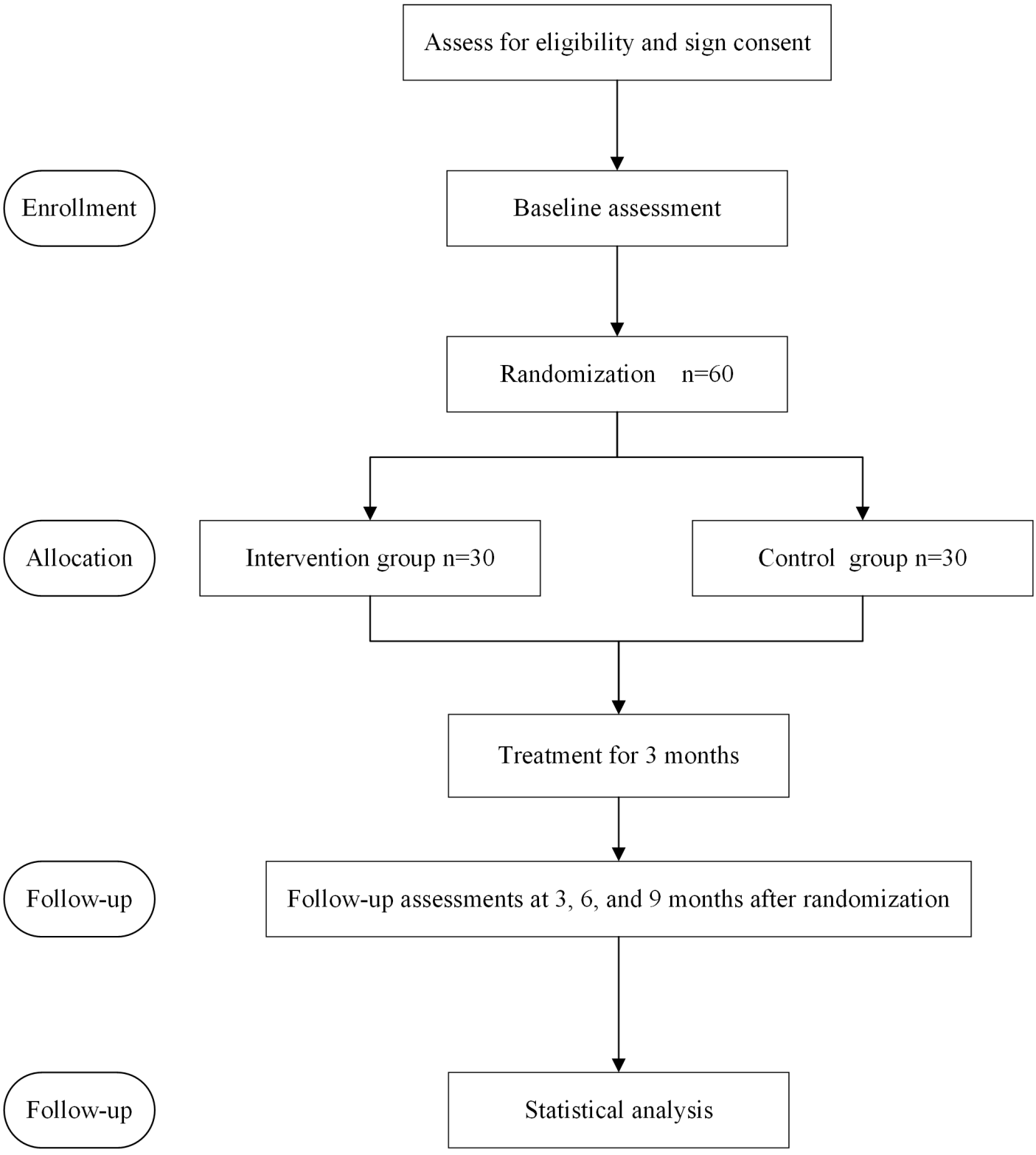

Figure 2

Trial profile.

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Closeout
TIMEPOINT	Day -7	Week 0	Week 4	Week 8	Week 12	Week 24	Week 36
ENROLMENT							
Eligibility screen	×						
Informed consent	×						
Randomization		×					
INTERVENTIONS							
Intervention group			←	—	→		
Control group			←	—	→		
ASSESSMENTS							
BP		×	×	×	×	×	×
Proportion of hypertension					×	×	×
BMI & waist circumference		×			×	×	×
IPAQ		×			×	×	×
SF-12		×			×	×	×
AEs		×			×	×	×

Figure 3

Schedule.

Supplementary Files

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