Informed Consent Form for Research Study

A Cohort Study on Increasing Blood Pressure Benefits in Sleep Apnea Patients After CPAP Treatment

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Study Title: Cohort Study on Enhancing Blood Pressure Benefits Following CPAP Therapy in Patients with Sleep Apnea

Sponsor: Beijing Anzhen Hospital Affiliated to Capital Medical University

Dear Participant:

You have been invited to participate in the Cohort Study on Enhancing Blood Pressure Benefits Following CPAP Therapy in Patients with Sleep Apnea. Please read this informed consent form carefully and make a deliberate decision regarding your participation in this study. When your study physician or researcher discusses this consent form with you, you may ask him/her to explain any parts you do not understand. We encourage you to discuss your decision to participate thoroughly with your family and friends before making a final choice. If you are currently participating in another study, please inform your study physician or researcher. The purpose, background, study process, and other important information regarding this study are as follows:

I. Background

The prevalence of hypertension among adults in China is approximately 27.9%. Among individuals with early-stage blood pressure abnormalities (130-139/80-89 mmHg), lifestyle interventions can reduce blood pressure to normal levels (<120/80 mmHg) in some cases. However, others fail to achieve normal blood pressure or experience further increases.

Obstructive sleep apnea (OSA) is a significant hypertension risk factor in China, affecting approximately 176 million individuals, including 67 million with moderate-to-severe disease. OSA elevates blood pressure through two pathways:

(1) Nocturnal upper airway obstruction causes intermittent hypoxia and autonomic nervous system disruption, triggering short-term blood pressure spikes;

(2) Sleep fragmentation increases daytime sympathetic activity, elevating diurnal blood pressure.

Continuous positive airway pressure (CPAP) is the mainstream treatment for OSA, but its blood pressure-lowering effect is limited:

(1) Meta-analyses show CPAP reduces 24-hour systolic blood pressure by only 3.55 mmHg;

(2) Ou et al. found no significant blood pressure improvement after 6 months of treatment.

II. Research Objectives

1. Validate novel sleep-blood pressure parameters for identifying OSA patients likely to benefit from CPAP-induced blood pressure reduction.

2. Identify reasons for suboptimal blood pressure improvement in OSA patients undergoing CPAP therapy through post-treatment analysis.

3. Improve CPAP treatment adherence and enhance blood pressure benefits by treating insomnia and post-CPAP arousals (including micro-arousals) with trazodone or zopiclone.

III. Study Process

1. How many people will participate in this study?

Approximately (200) participants will enroll across (1) distinct research institutions/medical centers. Approximately (200) participants will enroll at Beijing Anzhen Hospital, Capital Medical University.

2. Study Procedures

If you consent to participate, please sign this informed consent form.

Study Population: Participants will be recruited from Anzhen Hospital's Sleep Medicine Center and

Hypertension Department.

Inclusion Criteria:

- Aged 18-70 years;
- Diagnosed with obstructive sleep apnea (OSA) via overnight polysomnography (PSG), meeting one of the following criteria: (a) AHI ≥ 5 events/hour and at least one of the following: (1) Patient reports daytime sleepiness, unrefreshing sleep, fatigue, or insomnia; (2) Awakens from sleep due to gasping or choking; (3) Reports from bed partners or witnesses of habitual snoring, breathing interruptions, or both during sleep. Or (b) AHI ≥ 15 events/hour;
- Blood pressure meeting any of the following criteria: (1) Office blood pressure 120–139/80–89 mmHg with ≤2 cardiovascular risk factors; (2) Newly diagnosed blood pressure 140–159/90–99 mmHg without cardiovascular risk factors; (3) Hypertensive patients with low cardiovascular risk who are currently on stable antihypertensive medication but whose office blood pressure remains above normal standards (120/80 mmHg); (4) Any patient with non-high cardiovascular risk who voluntarily requests three months of non-antihypertensive medication therapy;
- Able to tolerate 24-hour ambulatory blood pressure monitoring and continuous blood pressure monitoring;
- Understands and signs the informed consent form, voluntarily agrees to undergo 3 months of CPAP therapy and participate in follow-up.

Exclusion Criteria:

- Previously diagnosed OSA currently undergoing OSA treatment (CPAP, orthopedic appliances, surgery, etc.);
- Secondary hypertension caused by conditions other than OSA, such as renal artery stenosis, nephropathy, Cushing's syndrome, or primary aldosteronism;

- Unstable medical condition (cardiovascular or cerebrovascular event or major surgery within the past 3 months, severe hypersomnia [ESS ≥ 16 points] or cognitive impairment preventing cooperation, active psychiatric illness, or substance/alcohol abuse);
- Rheumatic/autoimmune diseases and malignancies;
- Aortic diseases (e.g., aortitis, aortic dissection, aneurysms);
- Conditions precluding accurate blood pressure measurement (e.g., atrial fibrillation, upper extremity vascular disease);
- Familial early-onset hypertension;
- Any prescription or over-the-counter sleep aids within 4 weeks prior to enrollment (e.g., benzodiazepines, non-benzodiazepine hypnotics, melatonin receptor agonists, trazodone, sedative antidepressants/antipsychotics, sedative-containing OTC products);
- Allergy or contraindication to potential study drugs (trazodone, zopiclone);
- Pregnancy, breastfeeding, or planned pregnancy;
- Frequent night shift work (≥3 nights/week) or circadian rhythm disorder (medically diagnosed);
- Participation in other interventional clinical trials.

CPAP Intervention:

Subjects undergo CPAP therapy in fixed pressure mode, with ≥4 hours of use per night and ≥21 days of use per month. Prior to treatment initiation, subjects undergo overnight automated (or manual) pressure titration under PSG or overnight automated pressure titration without PSG, based on clinical condition, to select the optimal pressure achieving “optimal/good” therapeutic effect (referencing the American Academy of Sleep Medicine's CPAP Treatment and Titration Standards for Adult Obstructive Sleep Apnea). Investigators enhance subjects' understanding of CPAP

through educational outreach to overcome psychological barriers. During follow-up, respiratory and otolaryngology specialists addressed specialty-related issues affecting CPAP use, promptly resolving CPAP-related discomforts to enhance treatment adherence.

Pharmacological Intervention:

Study Component 3: Patients with OSA and insomnia or frequent awakenings during CPAP therapy were recommended combined CPAP and trazodone (or zopiclone) treatment. Treatment regimen: Take trazodone at an initial dose of 25-50 mg/night before bedtime. Based on patient tolerance and efficacy, the dose may be increased by 25 mg every 3-5 days, not exceeding a maximum of 150 mg/night. Zopiclone should start at 3.75-7.5 mg/night, adjustable to 7.5 mg/night as appropriate. The total treatment period is 4 weeks. Changes in subjective and objective sleep quality before and after medication are recorded using questionnaires, actigraphs, and polysomnography. During follow-up, patients are naturally grouped based on treatment choice and adherence: CPAP alone, CPAP plus trazodone, trazodone alone, or no treatment. Compare baseline-to-endpoint blood pressure changes across groups, including intra-group comparisons and inter-group rate comparisons.

3. How long will this study last?

Study 1 and Study 2 are expected to last approximately 3 months, while Study 3 is projected to last about 1 month.

You may withdraw from the study at any time without penalty and without forfeiting any benefits to which you are entitled. However, if you decide to withdraw during the study, we encourage you to first discuss this with your doctor. For your safety, a follow-up examination may be conducted after withdrawal.

IV. Risks and Benefits

1. What are the risks or adverse reactions associated with participating in this study?

Participation in this study may carry the following risks. You should discuss these risks with your study doctor or, if you prefer, with your regular doctor. During the study, you may experience some, all, or none of the following adverse reactions:

1. CPAP Treatment Component:

(1) Common Mild Discomfort:

- Mask Area Discomfort: Skin indentations, redness, or mild pain on the face/nose bridge (typically related to mask wear);

Respiratory tract dryness/irritation: Nasal/throat dryness, nasal congestion, runny nose, occasional nosebleeds (often alleviated by using a heated humidifier);

Initial discomfort: Feeling of mask stuffiness, machine noise or airflow sounds interfering with sleep (most patients gradually adapt);

Dry mouth (especially when breathing through the mouth);

(2) Rare but serious adverse reactions:

Significant gas accumulation in the gastrointestinal tract due to machine-delivered air (may cause abdominal discomfort or pain, usually resolved by adjusting therapy).

Extremely rare middle ear or eye discomfort related to air pressure (associated with abnormal gas leakage).

2. Medication section (Trazodone or Zopiclone):

(1) Common mild discomfort (may occur in most patients):

Daytime drowsiness, dizziness, or fatigue;

Dry mouth;

Headache;

Nausea;

(2) Rare but serious adverse reactions:

Trazodone: Extremely rare but noteworthy priapism (male patients should seek immediate medical attention if it occurs).

Zopiclone: Risk of drug dependence (with long-term use; this study is 4 weeks).

*(Particularly important for patients assigned to the “Trazodone alone group” not concurrently using CPAP): The medication may not adequately treat your sleep apnea and carries a potential risk of worsening nocturnal breathing issues (e.g., respiratory suppression).

3. General Study-Related Discomfort:

Minor inconvenience or occasional fatigue may occur from completing questionnaires or wearing actigraphs or polysomnography equipment.

2. What are the benefits of participating in the study?

If you agree to participate, you will receive regular follow-up care and treatment guidance from physicians to aid your recovery. We hope the information gathered from your participation will benefit future patients with similar conditions.

V. Will my information remain confidential?

The results of this study may be published in medical journals. We will strictly comply with the law to keep your research records and personal information confidential. Your information will not be disclosed except as required by law or authorized by regulatory bodies (such as ethics committees) in accordance with regulations.

VI. Research Costs and Related Compensation

1. Costs for medications and related examinations used in the study

(1) Material fees:

Polysomnography (PSG) consumables, ambulatory blood pressure monitoring (ABPM) consumables, experimental consumables.

(2) Test Processing Fees

24-hour ambulatory blood pressure monitoring, electronic questionnaire design and maintenance, routine blood/urine/stool tests, sputum analysis.

All above items are managed by the Sleep Medicine Center.

2. Compensation for Injuries

Should any injury occur related to this study, you will receive necessary medical care provided by the Sleep Medicine Center of Anzhen Hospital, Capital Medical University.
Compensation/damages will be determined in accordance with relevant Chinese laws and regulations following assessment by the responsible authorities.

VII. Subject Rights

Your participation throughout this study is entirely voluntary. Declining to participate will not affect other treatments you are entitled to receive. Should you decide to participate, you will be asked to sign this written informed consent form. You have the right to withdraw from the trial at any stage without facing discrimination or unfair treatment, and your corresponding medical care and rights will remain unaffected.

Should you experience a serious adverse reaction, or if your study physician determines continued participation is not in your best interest, he/she may decide to withdraw you from the study. The sponsor or regulatory authority may also terminate the study at any time during its course without requiring your consent. Should this occur, you will be promptly notified, and your study physician

will discuss alternative options available to you. No new data related to you will be collected, and your previously collected data will not be used for any scientific research.

VIII. Subject Responsibilities

As a subject, you are required to:

- Provide truthful information about your medical history and current physical condition;

- Inform the study doctor of any discomfort experienced during the study period;

- Refrain from taking any restricted medications, foods, etc., as advised by your doctor;

- Inform the study doctor if you have recently participated in other studies or are currently participating in other studies.

IX. Who should I contact if I have questions or difficulties?

For any questions related to this study, please contact Xie Jiang during business hours at 010-64456528. After hours, on weekends, or during holidays, please reach Xie Jiang at 131 6198 5564.

For any concerns regarding your rights/interests, to report difficulties, dissatisfaction, or worries encountered during study participation, or to provide feedback/suggestions about this study, contact the Ethics Committee of Beijing Anzhen Hospital Affiliated to Capital Medical University at 010-64456214.

Informed Consent Form

Researcher Disclosure Statement

"I have informed the subject about the background, purpose, procedures, risks, and benefits of the ‘Cohort Study on Enhancing Blood Pressure Benefits After CPAP Treatment in Patients with Sleep Apnea.’ I provided sufficient time for the subject to read the informed consent form and discuss it with others, and I answered all questions regarding the study. I have informed the subject that they may contact Dr. Xie Jiang/the physician at any time regarding research-related matters, and may contact the Anzhen Hospital Ethics Committee regarding issues related to their rights/interests, and have provided accurate contact information; I have informed the subject that they may withdraw from this study; I have informed the subject that they will receive a copy of this informed consent form bearing both my signature and theirs."

Researcher Signature for Informed Consent:

Date:

Subject Informed Consent Statement

"I have been informed of the background, purpose, procedures, risks, and benefits of the study titled ‘Cohort Study on Enhancing Blood Pressure Benefits Following CPAP Therapy in Patients with Sleep Apnea.’ I had sufficient time and opportunity to ask questions, and I am satisfied with the answers provided. I have also been informed of whom to contact if I have questions, wish to report difficulties or concerns, have suggestions for the study, seek further information, or wish to provide assistance to the study. I have read this informed consent form and agree to participate in this study. I understand that I may withdraw from this study at any time during its duration without providing any reason. I have been informed that I will receive a copy of this informed consent form bearing both my signature and the researcher's signature."

Subject Signature:

Date:

Subject Contact Phone Number:

(When the subject lacks or has insufficient capacity to give informed consent, add or replace with the following:)

Legal Guardian Signature:

Date: