Efficacy and safety of Tetramethylpyrazine (TMP) Phosphate on Pulmonary Hypertension: study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background: Tetramethylpyrazine (TMP), an active ingredient in the traditional Chinese herbal medicine Rhizoma Chuanxiong, has been used clinically for the prevention and treatment of cardiovascular disease. The benefits of TMP are largely attributed to its anti-oxidative and vasodilative properties. However, the efficacy of TMP in the treatment of pulmonary hypertension (PH) is unknown. We hypothesized that TMP may have a therapeutic effect in patients with PH.

Methods:

A randomized, single-blinded, clinical study with a TMP treatment group and a control group will be conducted to evaluate the efficacy and safety of TMP intervention in patients with PH. The recruitment target is 120 subjects meeting the following criteria: (i) At rest and at sea level, mean pulmonary artery pressure above 20 mmHg and pulmonary capillary wedge pressure below 15 mmHg; (ii) Type 1 or 4 PH in the stable phase; (iii) age 15–70 years; (iv) 6-minute walk distance between 100 and 450 meters; (v) lung function at level II, III, or IV according to WHO classification. Subjects will be assigned randomly into two groups at a ratio of 1:2 (control:TMP). Both groups will receive routine treatment, and the treatment group will also receive oral TMP (100 mg) three times a day for 16 weeks. All patients will be followed up for 4, 8, 12, and 16 weeks, and symptoms and patient compliance will be recorded.

Discussion:

We aim to determine the efficacy and safety of TMP for the treatment of PH.

Study registration:

ChiCTR1800018664, http://www.chictr.org.cn/edit.aspx?pid=31565&htm=4 (registered on 2 October 2018).

Background

Pulmonary hypertension (PH) is a serious condition characterized by sustained elevated mean pulmonary arterial pressure (mPAP) over 20 mmHg and the development of right heart hypertrophy, leading to cardiac failure and, ultimately, death. [1-4].With improvements in diagnostic techniques, PH is no longer a rare disease. According to the latest epidemiological data, the prevalence of PH is about 1% of the global population.[5] Although understanding of the pathophysiology and pathogenesis of PH has increased, and quality of life of patients has improved significantly through the use of targeted drugs, persistent high mortality rates indicate that these drugs delay the progression of the disease and alleviate symptoms but do not effectively prolong the life of the patients.[6-9] In addition, the use of effective drugs is limited by their high cost. Therefore, it is imperative to develop new and affordable medications with strong efficacy and safety profiles.

Given its anti-oxidative, anti-myocardial injury, and vasodilative effects [10-13], tetramethylpyrazine (TMP), a traditional Chinese herbal medicine, is widely used in the treatment of cardiovascular and cerebrovascular diseases [14-17]. The pathogenesis of PH involves oxidative stress, vascular inflammation, and imbalance of intracellular calcium homeostasis [18-20]. However, it has not yet been reported whether TMP has a therapeutic effect on PH. In our previous study, we showed that TMP intervention improves calcium imbalance in pulmonary artery smooth muscle cells (PASMCs) by modulating the expression of TRPC1, TRPC6, Kv1.5, and Kv2.1 in a rat model of PH, potentially reducing intracellular free calcium concentration ([Ca 2+]i) to reduce the contraction and proliferation of PASMCs and improving pulmonary distal arteriolar remodeling. Regulation of [Ca2+]i in PASMCs may therefore represent a target for the treatment of PH, providing a basis for the development of new therapies for this condition.

We therefore designed a 16-week randomized, double-blinded, clinically controlled study to examine the efficacy and safety of TMP phosphate for the treatment of PH.

Methods

Study design

We designed a study protocol for a randomized controlled study. Screening (Visit 0) was undertaken within 3 days prior to enrollment to assess eligibility and collect baseline data. Subjects who entered the primary screening were assessed for lung function, and those meeting all criteria were randomly assigned (2:1) into a TMP treatment group or a control group. Both groups received conventional treatment, and the TMP treatment group also received 100 mg oral TMP three times daily. Patients were followed up at 1 month after randomization (Visit 1), and then every month until end of treatment at 16 weeks. Data collected at Visit 0 included patient characteristics (name, sex, age), medical history, concomitant medications, laboratory and auxiliary examinations, and adverse events. Additionally, at each visit, medical history, medications, cardiac and pulmonary function, and adverse events will be collected. Additional items will be evaluated at Visits 2 and 4. A schedule of assessments is shown in Table 1. A study flow chart is shown in Figure 1.

Sampling

Based on the 6-minute walk distance (6MWD) as the main efficacy index, it is assumed that after treatment, the experimental group has an average distance of 60 m from the control group of 6 minutes, the standard deviation is 60 m, α is 0.05, and the efficacy is 90% (β is 0.10). The sample size is:

See supplemental files for the formula

q1 is the proportion of the experimental group, and q2 is the proportion of the control group, q1=2/3, q2=1/3, N≈107.

Assume that the sample shedding rate is 11%, the sample size is approximately 120 participants, comprising 40 patients with control, 80 patients in TMP group.

Study procedure

Eligibility criteria for enrollment

The selection of participants will be based on the following inclusion and exclusion criteria:

Inclusion criteria

1. In accordance with the diagnostic criteria for PH, mPAP measured by right cardiac catheterization above 20 mmHg and pulmonary capillary wedge pressure (PCWP) below 15 mmHg, at sea level and in a resting state.

2. Subjects with Type 1 or Type 4 PH classified according to the World Symposium on Pulmonary Hypertension (2015 ESC/ERS guideline.) [21] who are in a stable stage, including idiopathic PH, hereditary PH, PH induced by drugs or toxins, PH associated with connective tissue diseases or congenital heart diseases (with no surgery/intervention within the previous 6 months); and chronic thromboembolic PH (surgical treatment is preferred for patients with surgical indications. For patients who have PH after surgery, are without surgical indications, or are nonoperable ones, stabilization with anticoagulant drugs (such as warfarin) for at least 1 month prior to participation is required).

3. Age 15–70 years, male or female.

4. WHO PH functional classification II, IV, or V.

5. 6MWD of >100 m and <450 m at baseline.

6. Patients stable for at least 1 month after standard treatment, and patients who have not received treatment with interventional or surgical closure in the 6 months prior to participation.

7. Patient or his/her guardian agrees to participation of the patient in the study and provides written informed consent for participation.

Exclusion criteria

1. Absent or limited legal capacity.

2. Pregnant or lactating women.

3. Serious primary diseases in major organs.

4. Mental or physical disability preventing the completion of 6MWD.

5. Suspected or confirmed history of alcohol or substance abuse.

6. Known allergy to the components of the drug.

7. AST and ALT values above 3 times the upper limit of normal, or Ccr <50 ml/min.

8. Low systemic blood pressure (<90/50 mmHg) or uncontrolled hypertension (blood pressure >170/110 mmHg).

9. Prior use of the study drug and discontinuation or change in targeted drugs (e.g. endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and guanylate cyclase) in the 3 months prior to screening.

10. Presence of an active infectious disease such as hepatitis A, hepatitis B, AIDS, tuberculosis, or connective tissue diseases.

11. Presence of serious infection, especially pulmonary infections.

12. Shock or other hemodynamically unstable conditions.

13. Cirrhosis or portal hypertension caused by cirrhosis.

14. Severe bleeding or bleeding tendency such as active peptic ulcer, intracranial hemorrhage, trauma, or other bleeding events.

15. Acute or chronic organic diseases (except for dyspnea) or other conditions (such as limb diseases) which may result in the subject being unable to complete the study (especially the 6MWD).

16. Any other circumstances under which the investigator considers the patient to be unsuitable for participation in the study.

Withdrawal criteria

1. Subjects having poor compliance with the dosing regimen

2. Use or accidental use of foods or drugs that may impact test results during the treatment period (e.g., amirace, fenfluramine, dexfenfluramine, L-tryptophan, methamphetamine, and phenylflurazone)

3. Subjects with incomplete key data that may affect the statistical analysis.

Endpoint standards

1. Subjects experiencing serious adverse reactions leading to suspension or termination of treatment during the study

2. Subjects whose condition deteriorates during the study
3. Subjects who withdraw consent or are unable to complete the study because of other circumstances

4. Patients treated with targeted drugs for Type 1 or Type 4 PH prior to testing who stopped treatment with the targeted drug for any reason during the study and did not reinitiate treatment

5. Death (from PH or another cause).

Drugs and usage

Subjects satisfying all criteria are assigned (2:1) randomly into two groups as follows:
1. TMP treatment group: TMP 100 mg 3 times daily in addition to routine therapy.

2. Control group: routine therapy only.
TMP was produced by Livzon Pharmaceutical Group Inc. (Zhuhai, Guangdong Province, China), following the instructions of the People's Republic of China Pharmacopoeia [22]. Routine therapy does not differ between two groups, and included phosphodiesterase type 5 inhibitors (sildenafil and tadalafil). Where subjects have previously received targeted drugs for the treatment of PH, the regimen will remain unchanged.

Outcome measurements

Efficacy indicators
The main efficacy indicators are the 6MWD and heart rate recovery at 1 minute (HRR1) after the 6MWD (Table 2).

Secondary efficacy measurements include the following 12 indicators (Table 2): PH WHO Classification, Borg Dyspnea Score, Minnesota Living with Heart Failure Questionnaire (MLHFQ), NT-proBNP (N-terminal pro-brain natriuretic peptide), cTNI (cardiac troponin I), right ventricular systolic pressure (RVSP) evaluated by echocardiogram, uric acid, volume of pericardial effusion, pulmonary artery diameter assessed by CT, diameter of the same layer of aorta assessed by CT, arterial oxygen saturation, and time of clinical deterioration.

Safety evaluation

Symptoms and signs including respiration rate, heart rate, and blood pressure are recorded at each visit. Laboratory tests are performed within 3 days prior to enrollment, and include routine blood tests and urinalysis, liver function, renal function, coagulation function, and electrocardiography. Adverse events are assessed and then recorded in the CRF.

Evaluation of adverse events

Adverse events, including symptoms, signs, and physical or laboratory examination abnormalities, are carefully evaluated. All adverse events must be judged for their character, severity, and potential relationship to the study treatment. The correlation between adverse events and study treatment is divided into five levels: definite, probable, possible, unrelated.

Data management and statistical analyses

Data from each subject visit will be captured in the CRF.
Statistical analysis of the efficacy of the study will be performed using statistical data sets that met the protocol. The data will be analyzed by two-sided test t test, with categorical variables analyzed by $\chi 2$ test and rank variables by paired Wilcoxon rank sum test. The test level α is 0.05, and the P values ≤ 0.05 will be considered statistically significant.

Ethics

The present study is being conducted in accordance with the Declaration of Helsinki and relevant clinical study research regulations in China. The protocol was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. Prior to participation, all subjects must provide written informed consent.

Discussion

There is little evidence to date of the efficacy and safety of TMP therapy for PH. Targeted drugs with limited efficacy are expensive. The present clinical study is expected to provide evidence for the safety and efficacy of TMP, a new affordable potential treatment for PH.

Then plan to subsequently conduct a large-scale clinical study to comprehensively evaluate the efficacy and safety of TMP in the treatment of PH, based on the findings of the present study.

Study Status

Recruitment started in September 2018 and is planned to end in October 2018, with 120 patients randomized. Treatment with TMP is ongoing at present and expected to finish in October 2019. The current protocol version is 2.0, dated 28 September 2018.

List Of Abbreviations

6MWD: 6-minute walk distance, CRF: case report form, cTNI: cardiac troponin I, HRR1: heart rate recovery at 1 minute, Minnesota Living with Heart Failure Questionnaire: MLHFQ, NT-proBNP: N-terminal pro-brain natriuretic peptide, RVSP: right ventricular systolic pressure, WHO: World Health Organization, PH: pulmonary hypertension, TMP: tetramethylpyrazine.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. Prior to participation, all subjects must provide written informed consent.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JW is the coordinator of the study, WH wrote the first draft of the manuscript. YC was critically involved as co-principal investigator in the planning and the conduct of the study (application for funding and trial design) and in finalizing the manuscript. HOY and KY were involved in critically revising the manuscript. TW helped to finalize the manuscript. CH and CL were investigators at the clinical site. WL was responsible for planning all statistical analyses. All authors read and approved the final manuscript.

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Author Details

Not applicable.

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Tables

Table 1 Study schedule of assessments

Visit cycle evaluation projects	Screening stage	Visit 1	Visit 2	Visit 3	Visit 4
Time-Window	Day -3–0	Week 4	Week 8	Week 12	Week 16
Inclusion and exclusion criteria	√				
Informed consent	√				
Basic condition	√				
Basic medical history	√				
Complication	√	√	√	√	√
Symptoms and signs	√	√	√	√	√
Drug combination	√	√	√	√	√
Blood routine test, urine routine, liver and kidney function, coagulation function	√				√
Evaluation of cardiopulmonary function (6MWD, WHO-FC, Borg Score, MLHFQ)	√	√		√	√
Electrocardiogram	√				√
Imaging	√				
Arterial blood gases	√				√
NT-proBNP, cTNI levels	√				√
Echocardiography	√		√		√
Pulmonary function test	√		√		√
Adverse events		√	√	√	√

√, required

Basic medical history contains current medical history (symptoms and signs) and previous history

Evaluation of cardiac and pulmonary function includes a 6-minute walk distance (6MWD), Minnesota Living with Heart Failure Questionnaire (MLHFQ), Borg Score, and World Health Organization functional class (WHO-FC)

Safety parameters include routine blood tests and urinalysis, liver and kidney function, and coagulation function.

Table 2 Efficacy indicators

Main efficacy indicators	Secondary efficacy measurements
6MWD	Pulmonary Hypertension WHO Classification
HRR1	Borg Dyspnea Score
	Minnesota Living with Heart Failure Questionnaire
	NT-proBNP
	cTNI
	RVSP
	Uric acid
	Volume of pericardial effusion
	Pulmonary artery diameter
	Diameter of the same layer of aorta
	Arterial oxygen saturation
	Time of clinical deterioration

Clinical deterioration is defined as the need to increase medication or change the therapeutic regimen for the treatment of PH, particularly inhaled, intravenous, or subcutaneous application of prostacyclin and its analogues; aggravated symptoms of right heart failure that do not respond to diuretics; atrial septostomy or death; lung transplantation; or hospitalization caused by exacerbation of PH.

Other clinical symptoms and signs, biochemical indicators, and imaging indicators are recorded (Table 2) for comprehensive prognostic evaluation and risk assessment.

Figures

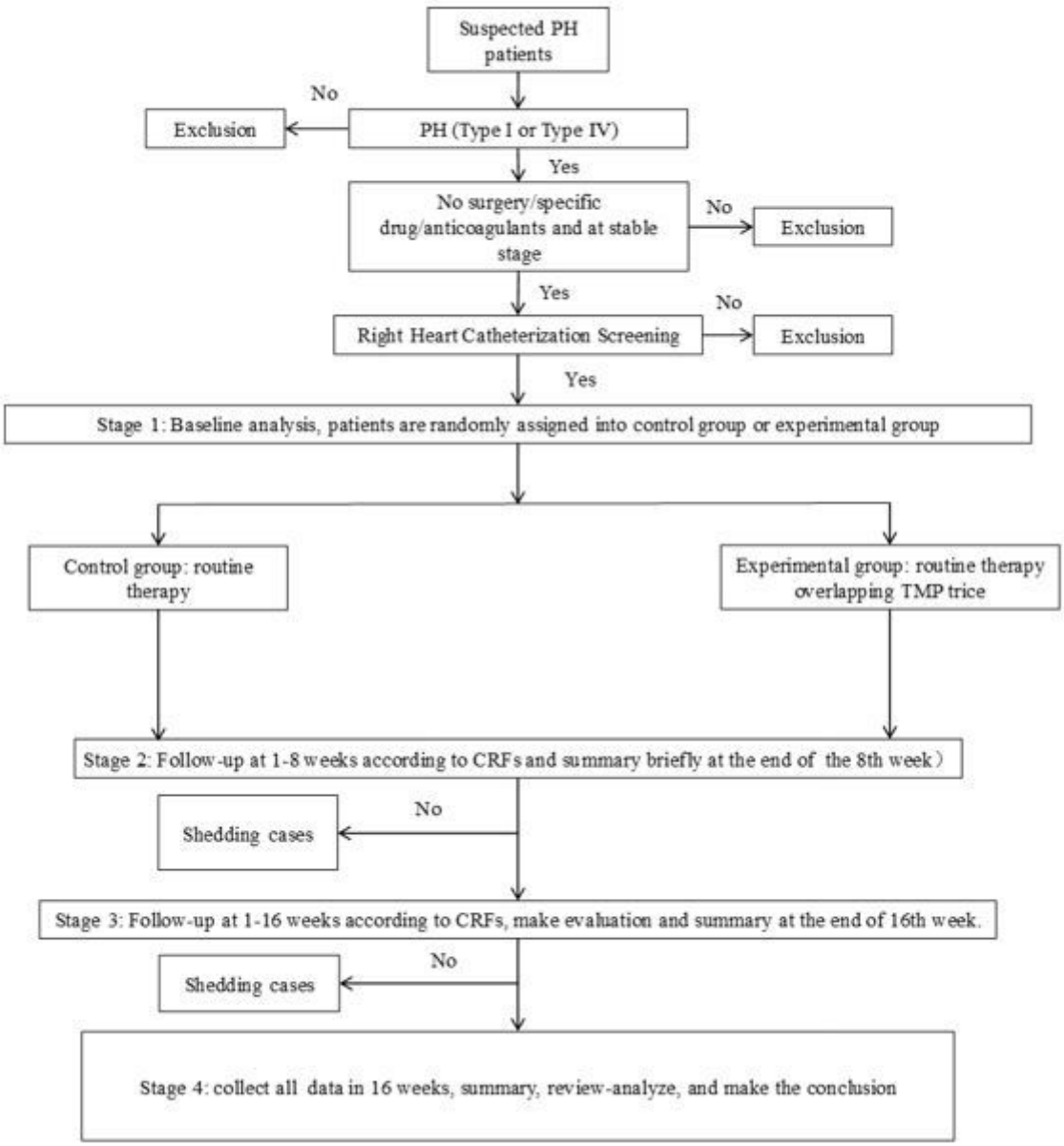

Figure 1

Flow chart for enrollment and follow-up of participants

Supplementary Files

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- supplement1.doc
- supplement4.jpg