Trimetazidine in angina and poor muscle function: protocol for a randomized controlled study

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Abstract

Background: Low handgrip strength (HS) and declining gait speed (GS) are increasingly obvious with aging, requiring effective, and safe medication for treatment. Trimetazidine (TMZ) modified release tablets, a common anti-angina drug, has potential benefits for alleviating the condition, but this has not yet been fully studied and therefore is the aim of this study.

Methods: This is a prospective randomized controlled study. Fifty-eight eligible patients will be randomly assigned to one of two study groups: TMZ group or control group. For the TMZ group, a dose of 35 mg of oral TMZ will be administered with a meal twice a day for 3 months, in addition to any conventional treatments for angina. Only conventional treatments for angina will be administered in the control group. The primary outcome will be the 6-min walking distance and the secondary outcomes will be: muscle strength (HS and pinch strength), GS, muscle endurance (five times sit-to-stand test), balance maintenance (tandem standing test), Additionally, body mass index, circumferences (biceps, waist, hip, and calf), albumin levels, and the score on a five-question scale for sarcopenia will be obtained during the study.

Discussion: This study aims to evaluate the usefulness of TMZ in a population with poor muscle function. The results may provide an effective and safe medical treatment to people with low muscle strength or physical performance.

Trial registration: Chinese Clinical Trial Registry, ChiCTR1800015000; www.chictr.org.cn/showproj.aspx?proj=25445.

Keywords: Trimetazidine; Angina; Strength; Physical performance

Introduction

Previous studies have shown that people aged more than 60 years old with low handgrip strength (HS, < 9 kg) accounted for nearly 10% to 20% of people in this age range, and the condition worsened with age. More than 50% of people aged more than 90 years old had low HS.¹ Another study, targeting people aged nearly 70 years old, found that nearly 45% of them had low gait speed (GS, < 0.7 m/s).²

Until now, there has been no effective and safe medicine, which is publicly accepted, as a treatment for low muscle strength or poor physical performance in elderly people. Trimetazidine (TMZ), a traditional anti-angina drug, targets both skeletal and cardiac muscle cells through the improvement of energy metabolism in both types of cells.³ Based on conventional therapies, TMZ could further improve cardiac function and muscle strength. Thus, exercise endurance could, in turn, be promoted.⁴

Several studies have demonstrated the effect of TMZ on physical performance or muscle endurance in patients with ischemic heart disease (IHD) or claudication.³⁻⁸ TMZ is a potentially beneficial therapy for people with muscle function disorders, but this has not yet been fully recognized. Thus, we designed this study to assess the efficacy and safety of TMZ treatment in elderly patients with stable angina and poor physical performance, compared with conventional treatments for stable angina. Our hypothesis is that TMZ can improve muscle strength, physical performance, and muscle endurance in elderly patients with stable angina.

The present article proposes a protocol for this clinical study consisting of a randomized controlled trial with TMZ in elderly patients with stable angina and poor physical performance.
Methods

Ethical approval

The study will be conducted in accordance with the principles of the Declaration of Helsinki and national regulations. The study protocol (version 3.0, April 15, 2018) was approved by the Research Ethics Committee (REC) of Chinese People’s Liberation Army General Hospital (No. S2017-144-03) and Zhengzhou Central Hospital, Zhengzhou University (No. 201802). The protocol will be sent by the investigators to REC for fast review, if any amendments are required. Signed informed consent forms (ICF) will be required before intervention. Every patient will be given both verbal and written information describing the nature and duration of the clinical study by the investigators. Enrolled patients will receive a new ICF after any amendments approved by REC.

Study design

TMZ in angina and poor muscle function (TAP) is a prospective randomized controlled study that will be conducted in two centers in China.

Fifty-eight eligible patients will be consecutively recruited, and randomised to one of two study groups: a TMZ group or a control group. The randomized number will be produced by the software Statistical Package for Social Sciences (SPSS, version 22.0; IBM Co., Chicago, IL, USA). The parameter for the initial random seed will be 2,000,000. Ten blocks will be allocated to the TMZ and control groups in total, each of which will be composed of 29 participants. Conventional treatments for angina, including anti-platelet drugs, β-blockers, statins, calcium channel blockers, and nitrates, will be used in the control group. Because no placebo is available, blinding is not feasible in this study.

Study participants

The patient inclusion criteria are: (1) more than 60 years of age; (2) ICF signature confirmed; (3) low HS (<26.0 kg for men and <18.0 kg for women) or low GS (<0.8 m/s) [9,10]; (4) stable angina (a history of coronary artery disease [CAD] diagnosed by coronary artery angiography, computed tomography angiography, or treadmill test and the same cause, nature, location, duration, remission, and frequency of angina during the previous 3 months). [13] The exclusion criteria are: (1) secondary hypertension; (2) secondary poor muscle strength or physical performance, including New York Heart Association class III and class IV heart failures; (3) an operation in the previous 3 months or poor exercise performance caused by neurological diseases, musculoskeletal diseases or pain; (4) liver or renal dysfunction; (5) diagnosed thyroid diseases; (6) diagnosed hematomatological diseases; (7) diagnosed unhealed tuberculosis or metastatic advanced tumor or malignant tumor discovery <5 years ago; (8) being hypersensitive to TMZ or having taken TMZ in the previous 3 months; and (9) cannot cooperate well because of other comorbidities.

Unfit patients will be required to leave the study during the follow-up period. The elimination criteria are: (1) misdiagnosis; (2) false inclusion; (3) poor compliance (<80% or >120%); (4) critical protocol deviations (PDs); (5) disposal of medicine before Visit 1; (6) no data record after randomization; (7) concomitant other drugs that may improve muscle strength, such as androgens or creatines; (8) withdrawal of the ICF. The suspension criteria are: (1) critical safety issues that require the change to other drugs for treatment; (2) major PD that makes it difficult to assess the effect of TMZ; (3) intolerant adverse drug reactions (ADRs), such as headache, dizziness, stomachache, diarrhea, dyspepsia, nausea, vomiting, rash, pruritus, or urticaria; (4) death-caused treatment discontinuance; and (5) study cancelled for poor finance or management.

Sample size calculation

The sample size for the study was calculated using the formula: \[ n = \frac{2 \times (\mu_1 + \mu_2) + 2 \sqrt{2} \delta^2}{\bar{d}^2} \] (\( n \) means numbers of TMZ or control group, \( \alpha = 0.05, \beta = 0.1, t \) refers to Student test value, \( S \) refers to the standard deviation, and \( \delta \) indicates the permissible error) and the following statistical assumptions, as found in a previous study [10]: the increases in 6-min walking distance (6MWD) during intervention in the TMZ group and the control group were 38.3 ± 16.9 m and 24.8 ± 12.2 m, respectively. To determine a significant difference between the two groups, a type 1 error of 0.05 (α value), a power of 90% (1 - β value) and 1:1 case to control ratio were assumed. Power analysis and sample size software (version 11.0, PASS, NCSS LCC, Kaysville, UT, USA) were used for calculating the number of participants required. The calculated number of participants was 46, but anticipating a 20% drop-out rate and the allocation needs for two centers, 58 participants will be sufficient for the study.

TMZ treatments

TMZ (modified release tablets, Servier Pharma, Orléans, France) will be sealed at 30°C. In the TMZ group, a dose of 35 mg of oral TMZ will be administered with a meal twice a day, in addition to conventional treatments for angina, for 3 months. All drug packages will be returned to the investigators on time in every hospital visit.

Concomitant treatments

Concomitant treatments include anti-platelet drugs, β blockers, statins, calcium channel blockers, nitrates, oral anticoagulants, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers.

Planned visit schedule

All subjects will undergo a systemic muscle function evaluation, including medical history, physical performance, muscle strength, muscle endurance, a five-question scale for sarcopenia (SARC-F), and blood tests. All assessors will be trained at the project launch meeting.

The baseline data will be recorded on Day 0 after enrollment. The intervention will start on Day 1. There will
Table 1: Details of the planned visit schedule.

| Stage                   | Baseline (screening before intervention) | Follow-up period |
|-------------------------|------------------------------------------|------------------|
|                         | Day 0                                     | Day 7 ± 2        |
|                         |                                          | Day 30 ± 5       |
|                         |                                          | Day 60 ± 5       |
|                         |                                          | Day 90 ± 10      |
| Included or excluded    | X                                        | X                |
| Eliminated or suspended | X                                        | X                |
| Medical history         | X                                        | X                |
| Physical examination    | X                                        | X                |
| Blood routine test      | X                                        | X                |
| Biochemical test        | X                                        | X                |
| Scale assessment        | X                                        | X                |
| Concomitant drugs       | X                                        | X                |
| Drug disposition        | X                                        | X                |
| Compliance              | X                                        | X                |

1 Visit 1 and Visit 3 are phone visits and intervention will start after screening. 2 Medical history includes whether TMZ has been taken or operation has been performed during the past 3 months, whether hypersensitive to TMZ contents, and the frequency of angina in the past 3 months. 3 Physical examinations include height, body mass, circumference (biceps, waist, hip, and calf), muscle strength (HS and pinch strength), physical performance (6MWD and GS), and muscle endurance (FTSST and TST). 4 Biochemical test parameters include ALT, AST, Scr, Alb, and so on. 5 Scale assessment refers to SARC-F. 6 ADRs include headache, dizzy, stomachache, diarrhea, dyspepsia, nausea, vomiting, rash, pruritus, and urticaria. 7 Concomitant drugs mainly include statins, ACEIs or ARBs, and coenzyme Q10. Symbol “x” means inspection items in each stage. ACEI: Angiotensin converting enzyme inhibitors; ADRs: Adverse drug reactions; Alb: Albumin; ALT: Alanine transaminase; ARB: Angiotensin II receptor blockers; AST: Aspartate transaminase; FTSST: Five times sit-to-stand test; GS: Gait speed; HS: Handgrip strength; ICF: Informed consent form; 6MWD: 6-min walking distance; Scr: Serum creatine; TMZ: Trimetazidine; TST: Tandem standing test; SARC-F: Five-question scale for sarcopenia.

Muscle strength

Muscle strength includes HS and pinch strength measured by a dynamometer and a gauge, respectively (JAMAR 5030KIT; Sammons Preston Inc, Bolingbrook, IL, USA). The dominant hand will be ascertained by first testing the HS for each hand. After setting the adjustable dynamometer’s handle to the desired spacing (second handle position), participants will be asked to sit with the shoulder adducted and neutrally rotated, the elbow flexed at 90°, the forearm in a neutral position, and the wrist between 0° and 30° dorsiflexion and between 0° and 15° ulnar deviation, to grip the hand dynamometer.[13] Medical workers will lightly hold the readout dial to prevent inadvertent dropping and then say, “Squeeze as hard as you can . . . harder . . . harder . . . relax.” The tests will be carried out once for each hand. The hand with the highest value will be considered the dominant one. The dominant hand will be tested again at least 2 min later. The higher of the two measurements will be taken as the HS measurement. If the difference between the two hands is <1 kg, the right HS will be considered as dominant HS.

The test sites need to be roomy enough to accommodate medical workers and subjects. There should be no barrier on the walkway. If any assistance is needed for the test, or if subjects cannot complete the test in time, this will be recorded.

Physical performance

Physical performance includes 6MWD and GS. The start point, 3-m point, 9-m point, and the end point of a 12-m straight-line distance, measured by a tape, will be labeled with colorful plasters. Timing with a stopwatch will start when subjects reach the 3-m point and will end when the 9-m point is reached at normal GS.[12] The measurement will be carried out twice and the interval between one measurement and the next will be at least 5 min. The quickest time (rounded up to the nearest tenth of a second) will be used to calculate the 6MWD and GS with the following equations:

\[ 6MWD (m) = 360 \times GS (m/s) \]

\[ GS (m/s) = 6 \times \text{time (s)} \]

The test sites need to be roomy enough to accommodate medical workers and subjects. There should be no barrier on the walkway. If any assistance is needed for the test, or if subjects cannot complete the test in time, this will be recorded.
possible, will be the method used. The dominant hand will be tested three times with an interval of at least 3 min between tests. The average of the three tests will be taken and rounded up to the nearest tenth of a kilogram.

**Muscle endurance and balance maintenance**

Muscle endurance and balance maintenance assessment will comprise a five times sit-to-stand test (FTSST) and a tandem standing test (TST). The FTSST will be as follows: subjects will sit on a chair over 40 cm tall and place their feet on the ground with their arms crossed over their chests. Their backs will not be allowed to touch the back of the chair. The movement of five times sit-to-stand needs to be completed as quickly as possible. During the test, the arms have to stay still and the participants need to stand up straight. The test will be completed three times and the time for completion recorded with a stopwatch; an interval at least 2 min between each test will be allowed. The minimum time will be taken as the final result and will be rounded up to the nearest tenth of a second. If a participant needs to be supported by the arm for the sit-to-stand test, then this will be recorded at the time of the test.

For the TST, the dominant foot will be ascertained by a spontaneous answer to the question “which foot would kick out first when playing soccer.” A baluster will be equipped in the test places. In the TST test, subjects will wear comfortable flat shoes and have arms akimbo. Timing with a stopwatch will start when the toe of dominant foot is against the heel of the non-dominant foot and will end when the subject moves, seriously inclines or leans against the railing. The test will be repeated three times with an interval of at least 1 min between each measurement. The maximum time will be taken as the final result and will be rounded up to the nearest tenth of a second.

**Other physical examinations**

Body mass, height, and circumferences (biceps, waist, hip, and calf) will be measured to an accuracy of 0.1 kg or 0.1 cm, according to the standard protocols.

**SARC-F**

Several studies have demonstrated that SARC-F has a similar specificity in diagnosing sarcopenia as other definitions that require skeletal muscle mass measurement. There are five items in the questionnaire, and participants with a total score of four or more are classified as having sarcopenia.

**Blood tests**

Routine blood tests and biochemical tests will be carried out in the early morning before breakfast.

**Outcome variables**

The primary outcome variable will be the 6MWD change. The secondary outcome variables will be muscle strength (HS and pinch strength), GS, muscle endurance (FTSST) and balance maintenance (TST), and the change in the frequency of angina each week after medical administration.

**Safety variables**

Safety variables include the occurrence of clinical manifestations of ADRs, such as headache, dizziness, stomach-ache, diarrhea, dyspepsia, nausea, vomiting, rash, pruritus, or urticaria. Laboratory examination indicators, such as liver function and renal function, will also be taken into consideration.

**Adverse event management**

Adverse event (AE) is defined as any untoward medical occurrence in a patient administered with a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. Occurrences of AEs will begin to be collected and recorded by investigators after patients have signed the ICF. The post-therapy AE collection period will be defined as 30 days after the termination of TMZ. All AEs will be recorded in the case report form (CRF). Each AE will be evaluated for duration, severity, process, and causal relationship to the TMZ. The action taken with AE, the dose change of TMZ, the outcome and whether the event leads to termination will also be recorded. If serious AEs occur, including death, threats to life, hospitalization, or persistent or significant disability, it will be necessary to record the condition in CRF and report the matter to the principal investigator (PI), REC, and the China Food and Drug Administration within 24 h by telephone. All AEs occurring during the study will be followed up in accordance with good medical practice until resolved or judged no longer clinically significant.

**Statistical analysis**

Personal information (eg, name, address) will be confidential. All the information will be preserved at the two centers, after initial coding, and will be destroyed at the end of the study.

All the data will be analyzed using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA). A one-sided P value <0.05 will be considered statistically significant. All continuous variables will be checked for normal distribution with the Kolmogorov-Smirnov test. The variables under normal distribution will be expressed as the mean (standard deviation). The variables under skewed distribution will be expressed as the median (95% confidence interval). Categorical data will be expressed as the frequency (percentage). Student t test for normally distributed variables, the Mann-Whitney U test for skewed variables and the Chi-square test will be used to compare baseline data differences. Repeated measures variance analysis will be used to analyze the effect of TMZ on muscle strength, muscle endurance, and physical performance. No interim analyses will be applied in this study.
The study will be stopped when the PI sends the application form to the REC of Chinese People’s Liberation Army General Hospital.

Discussion

TAP will be the first multicenter, randomized, controlled study to test the hypothesis that TMZ can improve poor muscle function in stable angina patients.

Previous studies have indicated the potential role of TMZ in improving muscle status. A meta-analysis was performed to assess the efficacy of TMZ therapy on exercise endurance in patients with IHD. Sixteen randomized controlled trials consisting of 2004 participants were included. The results showed that TMZ significantly improved total exercise duration (TED), peak oxygen uptake, metabolic equivalent system, and performance in the 6MWD. In another study, 100 patients with claudication were enrolled in a 3-month parallel and double-blind study. Patients were randomized to receive TMZ or a matching placebo. All patients underwent a treadmill test, to evaluate maximal walking distance. Greater improvement was observed with the TMZ group compared with the placebo group (23% vs. 14%). Furthermore, a single center randomized and controlled trial recruited 60 patients with chronic heart failure. After 3 months of TMZ intervention, the TMZ group showed more improvement in 6MWD (an increment of 181 m vs. 129 m). Another single-center, randomized and controlled trial recruited 43 patients with stable angina. After 3 months of TMZ intervention, the TMZ group showed more improvement in TED (an increment of 2 min vs. 1 min). Although previous studies have demonstrated the effect of TMZ on physical performance or muscle endurance in patients with IHD or claudication, the role of TMZ in muscle function, has not been comprehensively and systematically evaluated.

In common with other TMZ studies, we have chosen 3 months as an adaptable action time to assess the efficacy of TMZ treatment, but our study design has additional distinctive features. In our study, the research subjects will be elderly people with stable angina and poor strength or physical performance. Stable angina is a typical indication to TMZ but, until now, less attention has been given to examines of muscle function. A further advantage of our study is that the daily dose of TMZ modified release tablets will be 70 mg (35 mg bid), 10 mg more than traditional TMZ tablets (20 mg tid) used in other studies.

Considering that additional supplements of androgens may increase the incidence of prostate cancers in the elderly, TMZ is a temperate and safe drug for patients with CAD, with few ADRs found in the Phase IV study. Of course, our study has inevitable limitations. First, because it is an investigator-sponsored study, no placebo is supplied. The placebo effect cannot be excluded when drawing conclusions and blinding is infeasible in this study. Second, the sample size is not large and the follow-up period is not long enough for financial reasons. Last, we only consider muscle function and do not take muscle mass changes into consideration, because the facilities used to measure skeletal muscle mass are quite different in the two centers for this study, and we do not currently have a way to calibrate the different apparatuses with each other. Despite these limitations, the application of TMZ in elderly patients will provide important evidence for the treatment of low muscle strength or poor physical performance. A neutral result will give us a vital glimpse into sarcopenia medical research, and means that a large, long duration follow-up intervention study on TMZ is warranted to further analyze the efficacy and safety of TMZ treatment in elderly patients with sarcopenia.

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Conflicts of interest

None.

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