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Efficacy and safety of Ferrous iron on the prevention of Vascular cOgnitive impaiRment among patients with cerebral Infarction/TIA (FAVORITE): rationale and design of a multicentre randomised trial

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ABSTRACT

Background The incidence of vascular cognitive impairment (VCI) is high in patients suffering from ischaemic stroke or transient ischaemic attack (TIA) or with vascular risk factors. Effective prevention strategies for VCI remain limited. Anaemia or low haemoglobin was found as an independent risk factor for adverse outcomes after acute stroke. Anaemia or low haemoglobin was possibly associated with an increased risk of poststroke cognitive impairment. Whether supplement of ferrous iron to correct anaemia reduces the risk of VCI and improves adverse outcomes in patients with ischaemic cerebrovascular disease remains uncertain.

Aim We aim to introduce the design and rationale of the safety and efficacy of Ferrous iron on the prevention of Vascular cOgnitive impaiRment in patients with cerebral Infarction or TIA (FAVORITE) trial.

Design FAVORITE is a randomised, placebo-controlled, double-blind, multicentre trial that compares supplement of ferrous iron with placebo for recent minor stroke/TIA patients complicated with mild anaemia or iron deficiency: Ferrous succinate sustained-release tablet 0.2 g (corresponding to 70 mg of elemental iron) once daily after or during breakfast for 12 weeks or placebo with much the same colour, smell and size as ferrous iron once daily during or after breakfast for 12 weeks. All paticipants will be followed within the next year.

Study outcomes The primary effective outcome is the incidence of VCI at 3 months after randomisation and the primary safety outcome includes any gastrointestinal adverse event during 3 months.

Discussion The FAVORITE trial will clarify whether supplement of ferrous iron to correct low haemoglobin reduces the risk of VCI in patients with recent ischaemic stroke or TIA complicated with mild anaemia or iron deficiency compared with placebo.

Trial registration number NCT03891277

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anaemia or low haemoglobin was reported as an independent risk factor for vascular cognitive impairment (VCI) in patients with ischaemic stroke.

WHAT THIS STUDY ADDS

⇒ This study designs a randomised controlled trial trial to evaluate whether supplement of ferrous iron reduces the risk of VCI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study might provide a new intervention target for reducing the occurrence of VCI in the clinical practice.

INTRODUCTION AND RATIONALE

The incidence of vascular cognitive impairment (VCI) is as high as 21%–70% among 3 months to 1 year after stroke.[1 2] Meanwhile, imaging changes of ischaemic cerebrovascular disease (eg, multiple infarcts, microbleeds or white matter hyperintensities) combined with vascular risk factors predicted a significantly increased risk of VCI.[3 4] VCI has become a serious disease that affects the life quality of Chinese residents, causing a heavy social and economic burden. The lack of effective intervention strategies for VCI is a key clinical problem that seriously affects the outcome of patients with stroke.

Previous studies have shown that anaemia or low haemoglobin was an independent risk factor for adverse outcomes in patients with stroke.[5–7] Studies have reported that about 10%–26% of hospitalised patients with acute stroke were identified as anaemia or iron

deficiency.[5–7] Our recent study with a total of 2240 patients with acute ischaemic stroke or transient ischaemic attack (TIA) within 7 days showed that patients with high baseline haemoglobin content were associated with a lower risk of poststroke cognitive impairment (PSCI) than those with anaemia (OR 0.64, 95% CI 0.43 to 0.94, p=0.02),[8] which suggested that low haemoglobin or iron deficiency might be involved in the development of VCI in patients with ischaemic cerebrovascular disease. Several clinical studies with small sample sizes have reported significant improvements in word learning and memory after iron supplementation in adolescent and childbearing women with iron deficiency,[9–11] which suggested iron supplementation as a potential treatment strategy for improving cognitive function. Whether supplement of ferrous iron to correct anaemia or low haemoglobin reduces the risk of VCI in patients with ischaemic cerebrovascular diseases remains unclear.

We hypothesised that iron supplementation to correct anaemia in patients with mild anaemia following recent ischaemic stroke/TIA could reduce the risk of VCI identified by Montreal Cognitive Assessment Scale (MoCA <26 scores) at 3 months/1 year after treatment.

Therefore, the ferrous iron on the prevention of Vascular cOgnitive impaiRment in patients with cerebral Infarction or TIA (FAVORITE) study was designed to check the above hypothesis. The aim of the study is to clarify the efficacy and safety of supplement of ferrous iron to correct haemoglobin deficiency and reduce the risk of VCI in patients with recent ischaemic stroke or TIA together with mild anaemia or low haemoglobin compared with placebo. This paper introduces the design and protocol of the FAVORITE trial.

METHODS

Study design

FAVORITE is a randomised, placebo-controlled, double-blind, multicentre trial. Patients with minor stroke (National Institute of Health Stroke Scale (NIHSS) ≤3 scores at the time of randomisation) or TIA within 3 months or chronic imaging changes of ischaemic cerebrovascular disease (eg, multiple infarcts, microbleeds or white matter hyperintensities) complicated with mild anaemia or low haemoglobin are randomised with 1:1 to ferrous succinate group or placebo group. All patients will be followed up for 3 months during intervention, and at 1 year after enrolment. The flow of the FAVORITE is displayed in figure 1. The study will recruit patients age ≥18 years with mild ischaemic stroke (NIHSS ≤3 scores) or transient ischaemic attack within 3 months or chronic imaging changes of multiple infarcts (≥2), multiple microbleeds (≥2) or white matter hyperintensities (Fazekas grading ≥2) showed on CT or MR without clinical events, complicated with mild anaemia or low haemoglobin. Patients are diagnosed with mild anaemia or low haemoglobin with haemoglobin concentrations 90–130 g/L for adult males and 90–120 g/L for adult non-pregnant females or serum ferritin <20 µg/L according to WHO criteria.[12–14] After randomisation, patients will be administrated with study drugs within 24 hours. The summary of inclusion and exclusion criteria is shown in figure 2. Each hospital has obtained institutional review board approval about the informed consent, protocol and other materials used to enrol patients prior to initiating the study. Patients from 20 centres from China will be screened and recruited in FAVORITE.

Randomisation

Subjects will be randomised (1:1) to receive either ferrous succinate or placebo. A randomisation sequence will be generated centrally using random permuted fixed-size block methods through SAS statistical analysis software V.9.4 (SAS Institute) from the Statistics and Data Centre at the China National Clinical Research Centre for Neurological Diseases. The randomisation computer programme will make the treatment assignment based

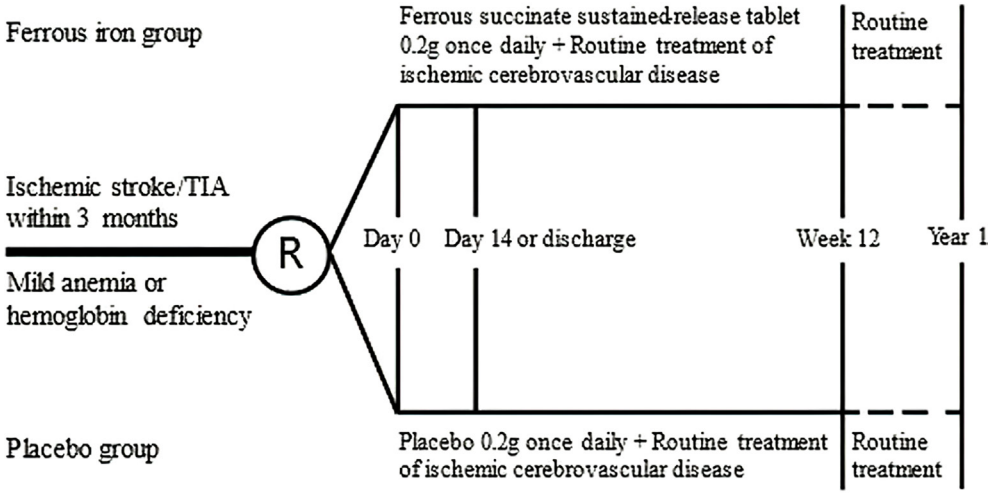

Figure 1 FAVORITE study design. FAVORITE, Ferrous iron on the prevention of Vascular cOgnitive impaiRment in patients with cerebral Infarction or TIA; TIA, transient ischaemic attack.

Inclusion criteria

1. Age 18~80 years old , male or female;
2. One of the following situations: A.recent minor ischemic stroke (NIHSS≤3 at the time of randomization) or TIA within 3 months; B. One or more vascular risk factors including hypertension, diabetes mellitus, or dyslipidemia, with multiple lacunar infarctions(≥2) or extensive white matter lesions(Fazekas grading ≥ 2) or multiple microhaemorrhage lesions(≥2) showed on CT or MR;
3. Fe deficiency (serum ferritin<20μg/L) or Hemoglobin deficiency (hemoglobin≥90 g/L and <120g/L or red blood cell count <4.0*10e12/L for female, hemoglobin ≥90 g/L and <130g/L or red blood cell count <4.5*10e12/L for male);
4. Informed consent signed.

Exclusion criteria

1. Intracranial haemorrhage or non -cerebrovascular disease (e.g. intracranial tumors, multiple sclerosis) on CT or MR;
2. Patients who can not cooperate with neuropsychological evaluation for severe hearing impairment, visual impairment, unilateral neglect, or dyskinesia;
3. Patients with moderate to severe anemia (hemoglobin<90 g/L);
4. Patients with thalassemia, megaloblastic anemia or erythronoclastic anemia, et al.
5. Patients with mental illness or schizophrenia;
6. Patients with chronic wasting diseases such as active tuberculosis and malignant tumor;
7. Patients who were diagnosed definitely as Alzheimer's disease , vascular dementia/vascular cognitive impairment, or other dementia;
8. Patients with history of taking drugs including Cholinesterase inhibitors, N -Methyl-D-aspartic acid antagonists, 5-hydroxytryptophan receptor antagonists, pyrrolidone or other drugs demonstrated as effective for improving cognition within 3 months before randomization;
9. Patients with severe liver or kidney insufficiency (Alanine transaminase>twofold upper normal limit or Aspartate Aminotransferase>twofold upper normal limit; Cr>1.5 times upper normal limit or Glomerular Filtration Rate<40 ml/min/1.73m2;
10. Patients with Severe urinary tract infection;
11. Patients with hemochromatosis or hemosiderosis(e.g. Iron lung deposition);
12. Patients with Iron allergy or other contraindications of using Iron;
13. Pregnant or Lactating women;
14. Patients who are undergoing other experimental drugs or device tests;
15. Patients unable to complete the follow-up of 3 months or 1 year due to geographical factor or other reasons;
16. Patients or legal representatives refuse to participate.

Figure 2 Summary of inclusion and exclusion criteria. NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.

on the overall balance of treatment assignment. After randomised allocation, the trial intervention will be administered to the participant as soon as possible.

Intervention

Ferrous succinate, as the most commonly used and the most accessible iron supplement for iron-deficiency anaemia in Chinese patients, is selected as the intervention medicine in this study with the conventional therapeutic dose of 0.2 g per day for 12 weeks.

Eligible patients are randomly assigned to each of two groups:

Ferrous succinate group

Ferrous succinate sustained-release tablet 0.2 g (corresponding to 70 mg of elemental iron) once daily after or during breakfast for 12 weeks.

Placebo group

Placebo tablets are made to be much the same colour, smell, size and as ferrous iron and are administrated once daily during or after breakfast for 12 weeks.

When the study period is over at the end of 12th week, the physician will decide whether ferrous iron is to be continued by the reviewed haemoglobin or serum iron level. The iron supplement will be suggested to continue if the reviewed haemoglobin <120 g/L or serum ferritin <20 µg/L. All patients will be followed up for 1 year.

Primary outcomes

The primary efficacy outcome is the incidence of VCI within 3 months after randomisation. The patients were evaluated by the MOCA through face-to-face follow-up in the outpatient clinic at 3 months±7 days. Patients are diagnosed with VCI with the criteria of MOCA<26 scores.[15 16] We also identify mild cognitive impairment or vascular dementia with other criteria including Clinical Dementia rating (CDR), Peterson's diagnostic criteria or DSM-V diagnostic criteria.[17 18]

Secondary outcomes

Secondary outcomes include (1) Incidence of VCI within 1 year (evaluated by the MoCA through face-to-face follow-up at 1 year±14 days, MoCA<26 scores is diagnosed as VCI); (2) Any new ischaemic stroke, TIA or haemorrhagic stroke events during 3 months and 1 year; (3) Any death during 3 months and 1 year; (4) Incidence of dependence during 3 months and 1 year (modified Rankin Scores≥3) and (5) The change of haemoglobin concentration, serum ferritin, red blood cell indices and the expression of key blood biomarkers including P-tau, amyloid protein β, that is, between the two groups.

The influence on treatment outcome of gender, age, time from index event to randomisation (≤14 days, 14 days ~3months or without ischaemic event but showing ischaemic cerebrovascular imaging changes, aetiology subtype, smoking, diabetes mellitus, dyslipidaemia and different levels of haemoglobin at randomisation will be clarified in the subgroup analyses.

Safety outcomes

The primary safety outcomes are (1) any gastrointestinal adverse event within 3 months, including abdominal pain, nausea, vomiting, diarrhoea, constipation or other gastrointestinal adverse events/serious adverse events (SAEs), excluded those independent of the supplementation protocol and (2) iron overload identified as serum ferritin exceeding 1000 µg/L within 3 months. Iron is deposited excessively in the body and causes structural damage and dysfunction of important organs (such as the heart, liver and joints).

Data safety and monitoring board

The data safety and monitoring board (DSMB) will monitor the progress of the trial and per protocol, ensure patient safety and ethically conduct of the trial. After each meeting, DSMB will provide recommendations in a written statement to the Chairs of trial Steering Committee. The responsibilities of members of DSMB are confirmed by the executive committee. They do not participate in the trial

Training and certification

The executive committee shall ensure that all subcentres investigators have received Good Clinical Practice training. Training should also be conducted on patient screening, follow-up and outcome evaluation for investigators in all subcentres (eg, NIHSS scores, mRS, MMSE, MoCA and CDR). Prior to study initiation, the principal investigators and coordinators of the subcentre will complete training and obtain certification as required.

Sample size

The sample size calculation is based on the risk of primary outcome (3-month risk of VCI). We applied the following assumptions: a significance level of 0.05 for a two-sided test; statistical power of 90%; according to the previous studies, the risk of VCI within 3 months after ischaemic cerebrovascular disease is 21%–70%, it is conservatively estimated that the risk of VCI within 3 months in patients with ischaemic cerebrovascular disease combined with iron deficiency or haemoglobin deficiency is 45% in the control group.[1 2] According to the previous studies, the relative improvement rate of iron treatment for cognitive impairment in patients with iron deficiency is about 25%,[9–11] and it is conservatively estimated that the 3-month risk of VCI in patients with ischaemic cerebrovascular disease combined with iron deficiency or haemoglobin deficiency treated by iron supplementation is 35%. Proportional risk reduction of 25% (rate ratio=0.75). We estimated that 1006 eligible patients (503 for each arm) are required. As 20% of patients are mild anaemia or low haemoglobin,[4 5] we will screen about 5030 patients in total.

Statistical analyses

The intention-to-treat analysis will be performed for all participants randomised to two groups. Subjects will be censored at their last follow-up review, at the time of

withdrawal from the trial or experiencing a clinical event. Multivariate analysis of VCI will be performed using a generalised linear model, with relative ratio (RR) and 95% CI calculated. Kaplan-Meier model will be used to evaluate the survival curve of all-cause death and stroke recurrence. The Cox proportional hazards model will be used to analyse all-cause death and stroke recurrence events for HR calculation and 95% CIs. Logistic regression model will be used to analyse outcome of dependence for OR calculation and 95% CIs. Statistical significance for primary outcome will be ascertained as p value of 0.05.

Study organisation

The trial steering committee will meet twice yearly and provides strategic input and oversight. The trial management committee executes the trial on a day-to-day basis and is based at the FAVORITE Trial Coordinating Centre. Trained assessors will analyse the outcomes, SAEs and imaging materials, masked to treatment assignment.

Study current stage

The enrolment had been completed on 1 March 2022. All the 3-month follow-up had been completed on 1 July 2022. All the 1-year follow-up had been completed on 1 June 2023. Now we are in the process of data cleaning and statistical analysis.

Limitation

We acknowledge several limitations of this study. (1) Previous studies on the effects of iron supplementation to correct anaemia on VCI were lacking, and the estimate of the relative proportion of improvement in the incidence of VCI in this study may be inaccurate, which may have a certain impact on the estimate of the sample size of this study. (2) Only patients with ischaemic cerebrovascular disease complicated with mild iron-deficiency anaemia were included in this study, and moderate and severe iron-deficiency anaemia were not included, which may have a certain selection bias on the outcome of improving cognition function with iron supplementation.

DISCUSSION

FAVORITE will address a major issue in the prevention of VCI with ferrous iron among patients with recent ischaemic stroke or TIA complicated with anaemia or low haemoglobin. The safety and efficacy of ferrous succinate will be assessed.

VCI refers to a series of syndromes with mild to severe cognitive impairment caused by cerebrovascular disease and its risk factors.[15 19] Clinical epidemiological data showed that the incidence of VCI was as high as 21%–70% within 3 months to 1 year after stroke.[1 2] The lack of effective intervention strategies for VCI is a key clinical problem that seriously affects the quality of life and outcome of patients with PSCI. Anaemia accounts for 10%–26% of acute stroke hospitalisations.[5–7] Common anaemia causes include high consumption after stroke, nutrient deficiency, reduced intake, peptic ulcers and use of aspirin or NSAID.[5–7] Data from the Third China National Stroke Registry-III showed that anaemia was associated with the higher risk of mortality and poor functional outcome in patients with acute ischaemic stroke or TIA.[7] Our previous study reported a total of 2240 patients with acute ischaemic stroke or TIA within 7 days and showed that after adjusting for other confounders, patients with high baseline haemoglobin content were associated with a lower risk of PSCI than those with anaemia (OR 0.64, 95% CI 0.43 to 0.94, p=0.02).[8] We observed clinically that systemic iron deficiency with various causes impaired cognitive function. The possible mechanism might include insufficient haemoglobin, decreased oxygen-carrying capacity of red blood cells, destruction of neurotransmitter synthesis and abnormal mitochondrial function in iron deficiency.[9 20] Several clinical studies with small sample sizes have reported significant improvements in word learning and memory after iron supplementation in adolescent and childbearing women with iron deficiency.[9–11] In high-risk VCI patients with ischaemic cerebrovascular disease complicated with anaemia or low haemoglobin, whether the application of iron supplementation to correct anaemia can improve outcomes and reduce the risk of VCI has not been reported. The FAVORITE trial is designed to evaluate the efficacy and safety of a supplement of ferrous iron to correct anaemia and reduces the risk of VCI in participants with recent ischaemic stroke or TIA together with mild anaemia or low haemoglobin compared with placebo.

SUMMARY AND CONCLUSIONS

The FAVORITE study will offer reliable data on whether a supplement with ferrous succinate is an effective and safe strategy compared with placebo for the prevention of VCI in patients with recent ischaemic stroke or TIA complicated with anaemia or low haemoglobin.

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Contributors QJ, PL, YilongW, XZ, YinkaiW and ZL contributed to the design of the study and contribute to its oversight. LS, WJ, YP, BY, XM, JJ, JL, YongjunW, QZ, AW, SZ, ZH, YX and YY coordinated the study. YongjunW and QJ wrote the first draft of the manuscript, which was edited by all other authors. Funding The Ministry of Science and Technology of the People's Republic of China (MOST) fund FAVORITE. This work was supported by grants from the National Key RandD Program of China (2018YFC1312300), and the National Science and Technology Major Project

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the FAVORITE trial was approved by ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2019-033-03) and all participating centres. Participants gave informed consent to participate in the study before taking part.

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