Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 108-117

Featured Article

Efficacy and safety of the compound Chinese medicine SaiLuoTong in vascular dementia: A randomized clinical trial

Jianping Jia[a,b,c,d,e,*], Cuibai Wei[a], Shuoqi Chen[a], Fangyu Li[a], Yi Tang[a], Wei Qin[a], Lu Shi[a], Min Gong[a], Hui Xu[a], Fang Li[f], Jia He[g], Haiqing Song[a], Shanshan Yang[h], Aihong Zhou[a], Fen Wang[a], Xiumei Zuo[a], Changbiao Chu[a], Junhua Liang[a], Longfei Jia[i], Serge Gauthier[j]

[a]*Innovation Center for Neurological Disorders, Department of Neurology, Xuan Wu Hospital, Capital Medical University, Beijing, China*
[b]*Beijing Key Laboratory of Geriatric Cognitive Disorders, Beijing, China*
[c]*Center of Alzheimer's Disease, Beijing Institute for Brain Disorders, Beijing, China*
[d]*Key Laboratory of Neurodegenerative Diseases, Ministry of Education, Beijing, China*
[e]*National Clinical Research Center for Geriatric Disorders, Beijing, China*
[f]*Department of Gerontology, Fuxing Hospital, Capital Medical University, Beijing, China*
[g]*Department of Health Statistics, Second Military Medical University, Shanghai, China*
[h]*Department of Neurology, Daqing Oilfield General Hospital, China*
[i]*Department of Neurology, Henry Ford Hospital, Detroit, MI, USA*
[j]*Centre for Studies in Aging, McGill University, Montreal, QC, Canada*

Abstract

Introduction: No licensed medications are available to treat vascular dementia (VaD).
Methods: Patients were randomly assigned to experimental groups (SaiLuoTong [SLT] 360 or 240 mg for groups A and B for 52 weeks, respectively) or placebo group (SLT 360 mg and 240 mg for group C only from weeks 27 to 52, respectively).
Results: Three hundred twenty-five patients were included in final analysis. At week 26, the difference in VaD Assessment Scale–cognitive subscale scores was 2.67 (95% confidence interval, 1.54 to 3.81) for groups A versus C, and 2.48 (1.34 to 3.62) for groups B versus C (both $P < .0001$). However, at week 52, no difference was observed among the groups on the VaD Assessment Scale–cognitive subscale ($P = .062$) because of the emerging efficacy of SLT in placebo beginning at week 27.
Discussion: This study suggests that SLT is effective for treatment of VaD, and this compound Chinese medicine may represent a better choice to treat VaD.

Keywords: Vascular dementia; Clinical trial; Compound Chinese medicine; SaiLuoTong/SLT

1. Background

Vascular dementia (VaD) is a cognitive dysfunction syndrome caused by ischemic stroke, hemorrhagic stroke, and cerebral vascular disease [1]. In China, the prevalence of VaD is 1.50% [2], and it is estimated that there are approximately three million patients with this disease [2,3]. Although acetylcholinesterase inhibitors, such as donepezil, galantamine, and rivastigmine, showed positive therapeutic effects on VaD in clinical trials, there are still no licensed medications that meet the criteria of the US Food and Drug Administration or the European Medicine Agency for this disease [1]. This requires that the drugs should show global or functional benefits, in addition to cognitive benefits, for approval [4,5]. In recent years, an increasing number of clinical trials have been conducted to

*Corresponding author. Tel.: 0086-10-83198730; Fax: 0086-83128678.
E-mail address: jjp@ccmu.edu.cn

https://doi.org/10.1016/j.trci.2018.02.004

test the effects of compound Chinese medicines for treating VaD, and many have shown positive effects by improving cognitive or behavioral symptoms [6].

The SaiLuoTong (SLT) capsule is a modern compound Chinese medicine that is manufactured by Shineway Pharmaceutical Group Co., Ltd (Shijiazhuang, China). It consists of active ingredients quantified in milligrams (for details, see eTable 1 in Supplementary 2) and derived from Ginkgo biloba, ginsenosides, and saffron in a 5:5:1 proportion per capsule, based on preclinical studies. Ginkgo biloba has antiinflammatory properties [7] and stimulates hippocampal neurogenesis [8]. Ginsenoside Rg1 inhibits oxidative stress-induced neuronal apoptosis [9], protects against neurodegeneration in cultured hippocampal neurons [10], and improves memory function in Alzheimer's disease (AD) and estrogen-deficient rat models [11,12]. Saffron has the capacity to scavenge oxygen free radicals [13], improve learning and memory in animal models of chronic stress [14], and alleviate neuronal injury *in vitro* and *in vivo* [15]. It also moderately inhibits acetylcholinesterase, which is the main effect of donepezil in AD [16], and a clinical trial showed that saffron has similar cognitive-enhancing effects to donepezil in patients with AD [16]. All of these functions of Ginkgo biloba, ginsenosides, and saffron in SLT are related to potential mechanisms that could help treat VaD.

Therefore, we hypothesized that SLT may have therapeutic efficacy in patients with mild-to-moderate VaD and designed the present clinical trial to test this.

2. Methods

2.1. Study design and participants

This 59-week, phase II, randomized, controlled, double-blind, parallel-arm study was performed at 16 academic centers throughout China. A protocol amendment was made on April 27, 2013, which increased the follow-up period from ± 1 week to ± 2 weeks for each visit to reduce the dropout rate. Fig. 1 displays an overall schematic of the design.

Eligible patients had to be aged ≥ 40 years, male or female, Han Chinese, have ≥ 5 years of education, have a diagnosis of probable VaD of mild to moderate severity, and have evidence of ischemic lesions on brain magnetic resonance imaging. Exclusion criteria were non-VaD primary dementia or non-ischemic VaD, disturbances of consciousness, severe aphasia, physical disabilities, or any other factor that could preclude the completion of neuropsychological testing. The full details of the inclusion and exclusion criteria are provided in eAppendix 1 in Supplementary 2.

The study protocol (Supplementary 1) was approved by independent ethics committees at all study sites. Written informed consent was obtained from each patient, or from the patient's legal guardian or representative, before enrollment. This study was registered at ClinicalTrials.gov (NCT01978730).

2.2. Randomization and masking

Randomization was performed using an interactive web response system and stratified according to severity of VaD (two levels: mild and moderate) and center (16 centers in total). Interactive web response system generated the randomization sequence with 33 blocks $\times$ 12 (4:4:2:2). The patient randomization file consisted of the trial randomization number and treatment group code. A drug kit number list was generated and subsequently assigned to the patients by interactive web response system. The personnel involved in the execution and data analysis were blinded to the drug kit randomization list. Study participants, their caregivers, and all assessors remained blinded to the treatment assignments throughout the study, and safety assessors were not permitted to be involved in the primary efficacy assessments. The SLT and placebo were identical in appearance, smell, and taste, to maintain blinding.

2.3. Study intervention

The trial began with a 1-week screening period and a 4-week placebo run-in period, and participants were randomly assigned to four groups: group A, SLT 360 mg, and group B, 240 mg SLT, for 52 weeks; group C (C1 and C2), placebo for the first 26 weeks and switched to SLT 360 mg and 240 mg, respectively, for the next 26 weeks (Fig. 1). Treatment compliance was monitored by counting the capsules. The number of capsules taken was recorded in a diary and reviewed at each clinic visit.

2.4. Primary and second outcomes

The coprimary outcomes included the Vascular Dementia Assessment Scale–cognitive subscale (VaDAS-cog) [17] and Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (ADCS-CGIC) scores [18]. The VaDAS-cog is composed of 14 items related to memory and orientation, language, the ability to practice, attention focus, and executive function (score ranges from 0 [no impairment] to 90 [serious impairment]). The ADCS-CGIC is a version of the clinician's interview-based impression of change plus caregiver input [19,20] and covers four domains (general, mental cognitive state, activities of daily living [ADLs], and behavior), with scores ranging from 1 (significant improvement) to 7 (severe deterioration). An experienced clinician performed the ADCS-CGIC and was blinded to all of the other psychometric assessments. The secondary outcomes included the Mini–Metal State Examination (MMSE), ADCS-ADLs, and Clinical Dementia Rating (CDR) scale scores, performance on the clock drawing task (CLOX) and the Chinese version of the executive interview (C-EXIT25), and the Neuropsychiatric Inventory (NPI). These scales evaluate global cognition, living ability, dementia