Effects of Chinese medicine for promoting blood circulation and removing blood stasis in treating patients with mild to moderate vascular dementia: a randomized, double-blind and parallel-controlled trial

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BACKGROUND: Vascular dementia (VaD) is the second common subtype of dementia after Alzheimer’s disease. However, there is still a lack of medication that demonstrates clinically relevant symptomatic improvement. Static blood obstructing the brain is the main Chinese medicine syndrome of VaD.

OBJECTIVE: To evaluate the effects of Chinese medicine for promoting blood circulation and removing blood stasis in patients with mild to moderate VaD.

DESIGN, SETTING, PARTICIPANTS AND INTERVENTIONS: In this 12-week randomized, double-blind, parallel-controlled trial, a total of 48 patients with mild to moderate VaD were enrolled between March 2009 and December 2010. All the patients entered a two-week placebo run-in phase followed by a 12-week treatment with Chinese medicine for promoting blood circulation and removing blood stasis (n=24) or placebo (n=24), respectively. The placebo tablets have the identical taste and appearance as the Chinese medicine tablets.

MAIN OUTCOME MEASURES: The primary outcome measure was the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog); the secondary outcome measures included...
the Activities of Daily Living (ADL) and the Mini-Mental State Examination (MMSE).

**RESULTS**: The Chinese medicine group showed a slight deterioration of 0.25 points and the placebo group showed a deterioration of 2.35 points from baseline by the ADAS-cog, and there was a significant difference between the two groups \( (P = 0.027) \). The ADL and the MMSE showed no significant difference from baseline in both groups. Adverse events were rare in both groups.

**CONCLUSION**: The Chinese medicine for promoting blood circulation and removing blood stasis may improve cognition and it is safe and well tolerated.

**KEYWORDS**: dementia, vascular; drugs, Chinese herbal; blood-activating stasis-removing agents; randomized controlled trial

Vascular dementia (VaD) is the second common subtype of dementia after Alzheimer’s disease (AD)\(^1\), and accounts for 15% to 25.5% of all cases of dementia worldwide\(^2\). The EURODEM Prevalence Research Group compared the prevalence of VaD in five datasets from Europe (Finland, Italy and Sweden and two from UK) and found that the prevalence ranged from 0.0% to 1.6% for those aged between 60 and 70 years and increased to 2.8% to 9.2% for those aged between 80 and 90 years. The annual incidence rate was estimated to be 3.79%. At present, the treatment of VaD focuses on primary and secondary prevention strategies, because randomized clinical trials in VaD have not been able to demonstrate clinically relevant symptomatic improvement, nor has it yet been possible to establish disease-modifying effects in VaD syndromes\(^3\). Hence, the development of an effective treatment for VaD is important and much needed.

Herbal medicine has long been used in China in the treatment of dementia. The Complete Work of Jingyue published in 1624 AD contains the earliest known description in the world of a herbal therapeutic strategy for dementia; herbal therapy may also be a new pathway for the treatment of AD\(^4\). Studies have shown that static blood obliterating the brain is the main Chinese medicine syndrome of vascular cognitive impairment\(^5\). Studies have shown that Chinese medicine protocols for promoting blood circulation and removing blood stasis can improve global cognition in patients with mild to moderate VaD\(^6\). However, at present, there are many limits in the clinical trials in Chinese medicine, such as a lack of uniform diagnostic and efficacy evaluation criteria.

The authors’ research group has developed a compound Chinese medicine for promoting blood circulation and removing blood stasis which is mainly composed of Danshen (Radix Salviae Miltiorrhizae) and Sanqi (Radix Notoginseng). Studies showed that Danshen extracts have neuroprotective effects via anti-free radical injury and regulating the content of glutamate and gamma\(^6\). Sanqi extracts can increase the concentrations of norepinephrine, dopamine and serotonin in the brain of mice with dementia\(^6\). In order to evaluate the efficacy of Chinese medicine protocols for promoting blood circulation and removing blood stasis in patients with VaD, the authors designed and conducted this randomized, double-blind, parallel-controlled trial.

1 Methods

1.1 Subjects This trial enrolled both outpatient and inpatient Chinese-speaking males and females between 45 and 80 years old, weighing between 45 and 90 kg, and meeting the diagnostic criteria for probable VaD established according to the Diagnostic

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and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)\textsuperscript{(16)} and the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN)\textsuperscript{(11)}. The diagnosis also had to be compatible with the findings from a recent (within last 12 months) magnetic resonance image (MRI) of the brain and with the Hachinski Ischemia Scale\textsuperscript{(12)} (HIS) score > 4. Inclusion criteria also required six months' mild to moderate VaD duration before inclusion. The severity of dementia was mild to moderate, and the score of the Mini-Mental State Examination (MMSE)\textsuperscript{(13)} was used to define the severity of dementia, which was defined as between 11 to 25, and had a score of \( \leq 12 \) of the Hamilton Depression Scale (HAMD for 17 items)\textsuperscript{(14)}. The score of static blood obstructing the brain syndrome in the scale for the differentiation of syndromes of vascular dementia was \( \geq 7 \) points\textsuperscript{(15)}. The patients must have adequate vision and hearing to participate in study assessments as well.

Patients who confirmed with any of the following exclusion criteria conditions were not enrolled for the study: subjects with AD and any other secondary types of dementia; depressive pseudo dementia and other mental disorders; a history of epilepsy; suffering from psychotic episodes; psychomotor excitation; a history of drug or alcohol abuse in the past six months; acute or uncontrolled chronic illnesses; a history of hypersensitivity to the treatment drugs; use of concomitant drugs with the potential to interfere with cognition; administration of other investigational drugs; use of oral anticoagulants; use of short-acting benzodiazepines; participation in other clinical studies.

The patients and their responsible caregivers provided written informed consent. The study was conducted according to the Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki. The institutional ethics boards of the Dongzhimen Hospital in Beijing approved the protocol.

1.2 Study design This study was designed as a randomized, double-blind, parallel, placebo-controlled trial. It consisted of a single-blind run-in and wash-out period using the placebo for only two weeks and a double-blind treatment phase after randomization for 12 weeks. During the two-week placebo wash-out period, all patients received the placebo of three tablets per dose, three doses per day. During the double-blind 12-week medication, the patients received the Chinese medicine protocol for promoting blood circulation and removing blood stasis or placebo (three doses per day, three tablets per dose). In order to preserve blinding, the placebo tablets had an identical taste and appearance to the Chinese medicine. Both the Chinese medicine protocol for promoting blood circulation and removing blood stasis, which mainly composed of Danshen and Sanqi, and the placebo were supplied by the Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited in China.

Concomitant use of other drugs was forbidden, which included anticonvulsant agents, anti-parkinsonian agents, antipsychotics, anxiolytics, hypnotic agents, neuroleptic agents, cholinomimetic agents, vitamin E, or ginkgo biloba extract or any other drugs that can affect memory. Administration of other drugs such as antihypertensive drugs, anti-diabetic drugs or antihyperlipidemics was permitted.

1.3 Randomization The randomization was stratified according to a center using the SAS statistic software. Patients were randomized in a ratio of 1 : 1 to receive the Chinese medicine tablets or placebo. The randomized code was generated in the randomization process and sealed in an envelope. Statisticians assigned the randomization code to the treatment drugs. Blinding was to be broken only if the patient’s trial medication would affect specific emergency treatment. Once the blinding was broken, the patient was managed as an off-case. Patients, caregivers, study investigators, and any other personnel involved in the study, and the investigative staff of the Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Company Limited remained blind until all patients accomplished the study and all databases were locked.

1.4 Efficacy measurements The neuropsychological assessments, laboratory determinations, measurements of vital signs (including body temperature, blood pressure and electrocardiogram) and neurological tests were evaluated before the patients were enrolled. All patients received an assessment at baseline (week 0) and endpoint (week 12), respectively. Any adverse events were recorded during the trial. The patients, therefore, received four clinical assessments in total.

The primary outcome measure was the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog)\textsuperscript{(16)}. The ADAS-cog contains 12 items, namely, dealing with word recall, naming objects and fingers, orientation, word recognition, spoken language ability, comprehension of spoken language, word-finding difficulty, construction, ideational praxis, following commands and attention. The scores of the ADAS-cog range from 0 to 75, and a higher score indicates a higher degree of impairment.

Secondary outcome measures included the MMSE and the Ability of Daily Living (ADL) scale\textsuperscript{(17)}. MMSE is used to assess the extent of cognitive dysfunction and the ADL is mainly used to measure the basic activities of daily living or self-care and the instrumental activities of daily living. The ADL scale can be divided to the Physical Self-Maintenance Scale (PSMS) and the Instrumental Activities of Daily Living (IADL). The PSMS relates to physical activities, such as toileting, mobility, dressing and bathing, and the IADL contains eight items, such as shopping, cooking, doing laundry, handling finances, using the telephone, using modes
of transport, being responsibility for own medication and housekeeping.

The VaD patients were assessed by two physicians. The two physicians participated in training in standard administration of the neuropsychological scales before commencing the trial.

1.5 Safety assessment The safety assessment was conducted at the baseline (week 0), and at the end of treatment (week 12). The safety assessment included: (1) physical examination items of vital signs, including breathing, heart rate and blood pressure; (2) electrocardiography; (3) laboratory testing (including urine and blood); (4) any adverse events which may occur.

1.6 Statistical analysis The statistical analysis was conducted using SPSS 17.0 software. The statistical analyses were planned to conduct in two populations. The intention-to-treat (ITT) population consisted of all the randomized population who took at least one dose of the medication and at least one primary efficacy evaluation on treatment. The safety set population included all randomized population who received at least one dose of the study medication, with at least one safety record at post-baseline. The efficacy analysis was conducted with the ITT population. The ADAS-cog was analyzed by using the Last Observation Carried Forward (LOCF) method for the replacement of missing observations. The occurrence of adverse events was analyzed using frequency calculations and descriptive statistics. The authors compared the demographic variables between the two groups by using Student’s t test and Chi-square test. Covariance analysis was used to compare means between the two groups at the 12th week. All reported incidence rates of adverse events between the two groups were detected by Pearson’s Chi-square test. P values were two-sided, and all analyses were significant if P values ≤ 0.05.

2 Results

2.1 Demographic data and baseline characteristics Of 155 patients screened, 48 patients received randomization, with 24 randomly allocated to placebo treatment, and 24 received Chinese medicine therapy. One patient did not have at least one post-baseline assessment and was excluded from the ITT population and safety population, and the remaining 24 subjects in the Chinese medicine group and 23 in the placebo group completed the study (Figure 1). The demographic characteristics of the subjects at baseline are summarized in Table 1. There were no significant differences between the two groups with respect to sex, race, education, height, age, weight and score of the neuropsychological assessment scales (P > 0.05).

2.2 Primary efficacy measurement In the total ITT population, after treatment for 12 weeks, there was a significant difference between the two study groups in the change of ADAS-cog total scores from baseline (P = 0.027). See Table 2. The mean ADAS-cog in the placebo group was significantly higher than the Chinese medicine group (P = 0.045). See Figure 2.

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**Figure 1 Flow diagram of the study population**
Table 1 Baseline demographic and clinical characteristics in patients with vascular dementia in the ITT population

<table>
<thead>
<tr>
<th>Index</th>
<th>Placebo (n=23)</th>
<th>Chinese medicine (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>62.5±8.5</td>
<td>66.9±7.0</td>
<td>0.088</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>16/8</td>
<td>16/8</td>
<td>1.00</td>
</tr>
<tr>
<td>Education (year)</td>
<td>8.6±1.0</td>
<td>8.1±1.4</td>
<td>0.160</td>
</tr>
<tr>
<td>Race (Han/others)</td>
<td>22/2</td>
<td>23/1</td>
<td>0.50</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.5±8.3</td>
<td>165.1±6.5</td>
<td>0.282</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.3±11.6</td>
<td>66.7±10.7</td>
<td>0.868</td>
</tr>
<tr>
<td>HIS score</td>
<td>11.08±2.19</td>
<td>11.13±1.83</td>
<td>0.975</td>
</tr>
<tr>
<td>MMSE score</td>
<td>22.96±2.71</td>
<td>22.92±2.24</td>
<td>0.766</td>
</tr>
<tr>
<td>HAMD score</td>
<td>4.79±4.23</td>
<td>4.96±4.34</td>
<td>0.983</td>
</tr>
<tr>
<td>ADAS-cog score</td>
<td>12.50±8.30</td>
<td>11.53±2.88</td>
<td>0.252</td>
</tr>
<tr>
<td>ADL score</td>
<td>20.67±9.26</td>
<td>19.40±6.87</td>
<td>0.502</td>
</tr>
<tr>
<td>SDSVD score</td>
<td>12.67±6.66</td>
<td>13.08±3.16</td>
<td>0.324</td>
</tr>
</tbody>
</table>

Data are expressed as mean±standard deviation or number. Comparison was conducted between the placebo group and the Chinese medicine group. ITT: intention-to-treat; HIS: Hachinski Ischemic Score; MMSE: Mini-Mental State Examination; HAMD: Hamilton Depression Rating Scale; ADAS-cog: Alzheimer’s Disease Assessment Scale-cognitive subscale; ADL: Activities of Daily Living; SDSVD: Scale for the Differentiation of Syndromes of Vascular Dementia.

Table 2 Change from baseline to endpoint on efficacy measures after 12 weeks in patients with vascular dementia by ITT-LOCF analyses (Mean±standard deviation)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>ADAS-cog</th>
<th>ADL</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>23</td>
<td>2.35±4.79</td>
<td>0.26±2.90</td>
<td>0.58±0.02</td>
</tr>
<tr>
<td>Chinese medicine</td>
<td>24</td>
<td>0.25±3.80*</td>
<td>1.04±3.51</td>
<td>0.38±1.50</td>
</tr>
</tbody>
</table>

*P<0.05, vs placebo group. ADAS-cog: Alzheimer’s Disease Assessment Scale-cognitive subscale; ADL: Activities of Daily Living; MMSE: Mini-Mental State Examination; ITT: intention-to-treat; LOCF: Last Observation Carried Forward.

Figure 2 ADAS-cog score at baseline and follow-up

ADAS-cog: Alzheimer’s Disease Assessment Scale-cognitive subscale.

2.3 Secondary efficacy measurements All secondary efficacy measurements were analyzed in the ITT population. At the study endpoint, the mean change of MMSE scores from baseline was 0.57 points in the placebo group and 0.38 points in the Chinese medicine group. There was no significant difference between the two treatment groups by ITT-LOCF analysis (P = 0.956). For the ADL, changes at study endpoint were similar in the two treatment group in the LOCF analysis of the ITT population. The mean increase of the ADL scores was 0.26 points in the placebo group and 1.04 points in the Chinese medicine group, and there was no significant difference between the two groups (P=0.902).

2.4 Safety and tolerability Chinese medicine protocol for promoting blood circulation and removing blood stasis was well tolerated throughout the study. During the study, there were four patients showing adverse events in the Chinese medicine group and two in the placebo group. In the Chinese medicine group, two suffered upper respiratory infection, which was considered to have no relationship with the Chinese medicine, and another two patients suffered stomach pain. In the placebo group, two patients had urinary system infection, which was considered to have no relationship with the placebo. And there was no significant difference between the two groups in the incidence of adverse events.

3 Discussion

The classical text Shanghanlun, pointed out that memory loss is associated with long-term blood stasis. This ancient theory was confirmed by a recent systematic review in which researchers found that the traditional Chinese syndromes seen in VaD are deficiency of kidney essence that constituted 66.67% of the patient population: static blood obstructing the brain, 50%; and the syndrome of phlegm, 44.4%[18]. The probable pathogenesis may occur in this way: the static blood obstructs the brain after stroke, and consequently affects memory and the patient’s daily function. Therefore, the authors used Chinese medicine with the function of promoting blood circulation and relieving blood stasis to treat VaD patients in this study.

Chinese medicine with the effects of promoting blood circulation and relieving blood stasis mainly includes Danshen and Sanqi. Studies showed that tanshinone can improve impaired learning and memory induced by Aβ42 in AD modal rats[19], reduce toxic free radicals, and suppress oxidative injury in AD rats[19]; salvianolic acid can inhibit the glutamate release, thus produce anti-cerebral ischemia effect[20]. In this randomized, double-blind, placebo-controlled study, compared with the baseline, although patients in the Chinese medicine group showed no significant changes in total cognitive function measured by ADAS-cog, the ITT population allocated to the placebo group had showed significant deterioration. While there was no significant difference between the two treatment group in the general cognition which was measured by MMSE, and ability of daily living which was measured by ADL.

Because the executive function may be particularly impaired in VaD, there is still debate that ADAS-cog may not sufficiently capture the specific deficits of executive function in VaD patients[21]. The ADAS-cog therefore may underestimate VaD patient...
function deficits. In the present study, by using the ADAS-cog as the primary outcome measure, it showed that a significant improvement of ADAS-cog total score was presented in the Chinese medicine group. Hence, ADAS-cog may also sensitive to measure the efficacy of treatment in patients with VaD.

Chinese medicine was well tolerated throughout the present study. Stomach pain was the most frequent adverse event in the Chinese medicine-treated patients, and there were no severe adverse events in both groups. Overall, Chinese medicine therapy showed a favorable safety and tolerability in patients with VaD.

Danshen extracts can significantly reduce platelet adhesion and inhibit platelet aggregation, thus affecting the process of hemostasis and promoting blood circulation, therefore, more attention should be paid when using such kind of Chinese medicine to promote blood circulation and remove blood stasis for patients with a bleeding tendency in clinical practice.

In summary, this study provides evidence on the therapeutic effects of Chinese medicine in patients with VaD. Moreover, Chinese medicine is generally safe and well tolerated in this study with 12 weeks' of treatment. However, there are several limitations in this study, which include the small sample size and a relatively short period of follow-up. Hence, further studies should be conducted on a large-scale population and to investigate the long-term therapeutic effects of Chinese medicine, as well as the effects of Chinese medicine in different subtypes of VaD.

4 Authors’ contributions

Tian was the study chair and was responsible for the conceiving and design of the study protocol, supervising analysis, interpretation of the data, and writing of the manuscript. Shi was the principal investigator for this study and assisted with design, drafting and revising of the manuscript. Wei and Ma conducted the clinical trial, and Wei prepared the draft of the manuscript. Mia conducted data analysis. Wang reviewed the design of the trial protocol. All the authors have read and approved the final manuscript.

5 Competing interests

The authors declare that they have no competing interests.

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活血化瘀中药治疗轻中度血管性痴呆的有效性：随机、双盲、安慰剂平行对照试验

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背景：血管性痴呆是继阿尔茨海默病后的第二大常见痴呆类型。随着人口的老龄化，其患病率逐步上升。但目前尚无有效且有效的药物，因此寻求中医药治疗是非常必要的。本研究旨在验证血管性痴呆的中医药证有效的中医证候。

目的：观察活血化瘀中药治疗轻中度血管性痴呆的临床疗效及安全性。

设计、场所、对象及干预措施：这是一项随机、双盲、安慰剂平行对照临床试验。自2009年3月至2010年12月共纳入48例轻中度血管性痴呆患者，随机分组为活血化瘀中药组(n=24)和安慰剂对照组(n=24)，所有患者接受2周的洗脱期，后分别分配为12周的活血化瘀中药治疗或安慰剂。安慰剂组气和外观均与活血化瘀中药不同。

主要结局指标：主要疗效指标是阿尔茨海默病评估量表（认知部分）(Alzheimer’s Disease Assessment Scale-cognitive subscale, ADAS-cog)；次要疗效指标是简易精神状态检查量表(Mini-Mental State Examination, MMSE)以及日常生活能力量表(Activities of Daily Living, ADL)。

结果：基线时两组人口学及神经心理学量表得分均无差异。活血化瘀中药组治疗12周后ADAS-cog得分较基线显著下降(P<0.05)，安慰剂组12周后ADAS-cog得分较基线显著升高2.35分，两组间ADAS-cog变化差的差异具有统计学意义(P=0.027)。两组间MMSE和ADL得分与基线比较差异无统计学意义。

结论：活血化瘀中药能维持患者认知功能，并且具有良好的安全性和耐受性，其远期疗效及安全性尚需大样本临床研究证实。

关键词：痴呆，血管性；中草药；活血祛瘀剂；随机对照试验