Int J Clin Exp Med 2018;11(4):4150-4155
www.ijcem.com /ISSN:1940-5901/IJCEM0073048

Original Article

Clinical effects of kidney tonifying granules on cognitive impairment and depression caused by cerebral small vessel disease

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Received January 19, 2018; Accepted February 23, 2018; Epub April 15, 2018; Published April 30, 2018

Abstract: Objective: To evaluate the feasibility and safety of using kidney tonifying granules plus western medicine for treating cognitive impairment and depression caused by cerebral small vessel disease (CSVD). Methods: Participants were 76 outpatients and inpatients with cognitive impairment caused by CSVD treated in Neurology Department of the Eighth People's Hospital of Shanghai during the time between February, 2015 and March, 2016. They were divided by random number table into two groups: the observation group and control group, each consisting of 38 patients. Both of the two groups received corresponding antihypertensive, hypoglycemic antihyperlipidemic and antithrombotic therapies and other basic treatments. Meanwhile, the observation group was given kidney tonifying granules plus nimodipine while the control group was given placebo plus nimodipine. Both of their treatment courses were 24 weeks. Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Self-Rating Depression Scale (SDS) scores and adverse drug reactions (ADR) scores of the two groups were compared. Results: Differences of baseline data of the two groups were of no statistical significance (P=0.429, P=0.612, P=0.823). At the 12th week, MMSE and MoCA scores of the two groups were obviously elevated compared with pre-therapy data (P=0.002, P=0.007, P=0.000, P=0.003). The observation group's scores went higher than the control group's (P=0.010, P=0.014). At the 24th week, those scores of the former group went much higher than that of the latter as well as that of themselves before taking the therapies (P=0.000, P=0.015, P=0.000, P=0.011). At the 12th week, the two groups' SDS score declined distinctly than their pre-therapy data (P=0.000, P=0.005) while the observation group's SDS score was even lower than the control group (P=0.008). At the 24th week, the observation group's SDS score went much lower than that of the control group as well as that of themselves before taking these therapies (both P=0.000). ADR rates of the two groups were respectively 23.68% and 18.42%, the difference of which was of no statistical significance (P=0.685). Conclusion: Kidney tonifying granules could help treat cognitive impairment and depression caused by CSVD. It is relatively safe and worth wide application.

Keywords: Kidney tonifying granules, cerebral small vessel disease, cognitive impairment, depression, safety

Introduction

Cerebral small vessel disease (CSVD) refers to a syndrome of strokes, cognitive emotions and overall dysfunctions (like voiding dysfunction, dysphoria and gait difficulty) caused by cerebral small vessel diseases. Jia et al. analyzed cases in the past 20 years and found out that CSVD accounted for 25%-50% of clinical strokes [1]. Vascular cognitive impairment caused by CSVD looks like normal aging as it is hard to discover and develops slowly. Thus, it is usually neglected by patients and patients' families. However, once it develops to vascular dementia, it is irreversible [2]. CSVD, on the other hand, is closely related to depression. Its pathogenesis might be associated with small vessel disease's damage on cortex-striatum - pallidum thalamocortical circuit [3]. Vascular depression not only slows down patients' neural functional recovery, pulls down patients' quality of life but probably also increase cerebrovascular diseases' disability rate, fatality rate and incidence rate of cognitive damage. To date, pathogenesis of CSVD is yet completely clear. For CSVD, there are mostly anti-dementia drugs and symptomatic treatments. There're no drugs specifically for it yet [4].

In recent years, there's an increasing amount of reports on Chinese medicines' effect on elevating cerebra metabolism and neurotransmitter

levels, improving antioxidant capacity of cerebral tissue and slowing hippocampal neurons' aging. Chinese medicines for dispersing of blood stasis and meridian regulations have special effect on treating cerebrovascular diseases such as cerebral infarction and cerebral hemorrhage. Xu et al., through CT cerebral perfusion imaging, discovered that blood stasis dispersing and meridian regulating soup was effective for neurological recovery of patients with acute cerebral infarction [5]. Experimental research also found that kidney tonifying soup could help improve rat's neurologic impairment [6]. Its pathogenesis might be accelerating VEGF expression inside ischemia cerebral cortex, thereby stimulating endogenous vascular generation. However, there're few reports on treatment of kidney tonifying granules on cognitive impairment and depression caused by CSVD. In this study, according to theory of traditional Chinese medicine on vascular cognitive impairment and depression, based on the pathology of such disease's blood stasis and obstructing the collaterals, we used kidney tonifying granules in addition to normal western medicine treatment, in hope of providing new direction and method for CSVD treatment by traditional Chinese medicines.

Clinical data

General data

Objects of this study were 76 outpatients and inpatients with cognitive impairment caused by CSVD treated in Neurology Department of the Eighth People's Hospital of Shanghai during the time between February, 2015 and March, 2016. Reference of western medicine diagnostic criteria were Rock-wood's diagnostic standard for vascular cognitive impairment and experts' consensus on diagnosis of CSVD published on *Chinese Journal of Internal Medicine* 2013 while reference of Chinese medicine diagnostic criteria were *Criteria of Diagnosis, Treatment and Effects of Traditional Chinese Medicines on Diseases and Symptoms* [7]. This research has been approved by the Ethics Committee of The Eighth People's Hospital of Shanghai.

Inclusion criteria: (1) In consistence with diagnostic criteria both by Chinese and Western medicine. (2) Montreal Cognitive Assessment (MoCA), scores <26. Add 1 score if the patient was educated for less than 12 years. Mini-Mental State Examination (MMSE), scores <23. If the patient received higher education, then scores ≤26. (3) Aged 45-80. (4) All the patients and their families were informed and consented and signed informed consent.

Exclusion criteria: (1) Patients with stroke records, and brain MRI test showed large area of infarction and bleeding; (2) Patients with intracranial space-occupying lesion and rapid progression of encephalatrophy; (3) Patients with severe speech, visual or hearing or spiritual disorder that affects cognitive test; (4) patients with severe heart, liver, kidney and Endocrine system and hematopoietic system diseases.

Methods

The observation group was given kidney tonifying granules (containing crude drugs: cistanche 20 g, lumbricus 12 g, the root of red-rooted salvia 10 g, radix curcumae 10 g, bitter cardamom 12 g) 1 packet/day + nimodipine (made by Huanan Pharmacy Co., Ltd.) 100 mg/day; and corresponding antihypertensive, hypoglycemic antihyperlipidemic and antithrombotic therapies and other basic treatments, whereas the control group was given placebo granules 1 packet/day + nimodipine 100 mg/day and corresponding antihypertensive, hypoglycemic antihyperlipidemic and antithrombotic therapies and other basic treatments. Treatment courses of the two groups were 24 weeks. Granules were provided by Tianjiang Pharmacy Co., Ltd.

Observation indicators

All the objects were required to accept outpatient follow up 1 time at the 12th and the 24th week. Follow ups included assessment questionnaire and oral inquiry of any clinical events or adverse drug reactions. 1) Cognitive function evaluation: 2 trained experienced professional clinical doctors testing the objects' mental health, in quiet environment at the same day, with the same MMSE and MoCA and standardized words. 2) Self-Rating Depression Scale (SDS) evaluation: SDS consisted of 20 items. Each item scaled 1-4 scores. Depression norm score in China is (41.88±10.57), and 53 is the threshold; 53-62 mild depression; 63-72 moderate depression and ≥73 severe depressions [8]. 3) Any adverse drug reactions (ADRs) like dizziness, headache, drowsiness, nausea and vomiting, thirsty and constipation.

Table 1. General data of the two groups

Group	Observation group	Control group	t	P
Case	38	38		
Gender				
Male/Female	22/16	20/18	0.623	0.429
Average age (years)	68.52±8.12	69.13±8.45	0.246	0.612
Education level			0.711	0.823
Junior secondary and technical secondary education	19	18		
High school and higher vocational education	11	13		
University degree or above	8	7		

Table 2. MMSE score comparison of the two groups at different time ($\bar{x}$ ±sd, score)

Group	Case	Pre-therapy	Therapy 12th	Therapy 24th
Observation group	38	18.912±4.067	23.113±2.575*,#	23.651±2.278*,#
Control group	38	19.012±3.782	21.282±2.661*	21.271±1.355*

Note: MMSE, Mini-Mental State Examination; compared with pre-therapy data, *P<0.05; compared with the control group, #P<0.05.

Table 3. MoCA score comparison of the two groups at different time ($\bar{x}$ ±sd, score)

Group	Case	Pre-therapy	Therapy 12th	Therapy 24th
Observation group	38	15.481±4.141	19.931±3.863*,#	20.442±1.233*,#
Control group	38	15.632±3.391	17.214±3.355*	17.163±1.960*

Note: MoCA, Montreal Cognitive Assessment; compared with pre-therapy data, *P<0.05; compared with the control group, #P<0.05.

Statistical methods

All the clinical data collected in this research were entered into Excel database and analyzed by two professional medical statistical researchers independently with SPSS 21.0. Education levels of the two independent samples were examined by Mann-Whitney U. Measurement data was examined by t and expressed by mean ± standard deviation ($\bar{x}$±sd) if it conformed to normal distribution while enumeration data was examined by chi-square test and expressed by rate (%). P≤0.05 means the differences were of statistical significance.

Results

General data

There were 82 objects in the study in total and 6 left, respectively 3 in each group. Objects filtered by inclusion and exclusion criteria were randomly divided into two groups, the observation group and control group. Each group consisted of 38 objects. In the observation group, there were 22 males and 16 females, aged 45-76, (68.52±8.12) year of age; 19 of them graduated from junior high school and technical secondary school, 11 from high school and vocational school and 8 from university and higher education institutes. In the control group, there were 20 males, 18 females, aged 46-78, (69.13±8.45) year of age; 18 of them graduated from junior high school and technical secondary school, 13 from high school and vocational school and 7 from university and higher education institutes. Differences of baseline data of the two groups were of no statistical significance (P=0.429, P=0.612, P=0.823). See **Table 1**.

Cognitive function

Before taking the therapies, differences of MMSE and MoCA scores of the two groups were of no statistical significance (P=0.812, P=0.912) while at the 12th week, these scores went distinctly higher than before (P=0.002, P=0.007, P=0.000, P=0.003) and the observation group's scores were higher than those of the control group (P=0.010, P=0.014). At the 24th week, the observation group's MMSE and MoCA scores went much higher than their pre-therapy data as well as those of the control group (P=0.000, P=0.015, P=0.000, P=0.011). See **Tables 2** and **3**.

Table 4. SDS score comparison of the two groups at different time ($\bar{x}$±sd, score)

Group	Case	Pre-therapy	Therapy 12th	Therapy 24th
Observation group	38	57.962±13.480	46.851±12.432*,#	39.673±9.682*,#
Control group	38	58.354±13.257	52.786±9.645*	55.452±11.188*

Note: SDS, Self-Rating Depression Scale; compared with pre-therapy data, *P<0.05; compared with the control group, #P<0.05.

Table 5. ADR comparison of the two groups (n, %)

Group	Observation group	Control group	χ^2	P
Case	38	38		
Dizziness and headache	2	1		
Drowsiness	2	1		
Nausea and vomiting	2	3		
Dry mouth and constipation	3	2		
Total incidence	9 (23.68)	7 (18.42)	0.046	0.685

Note: ADR, adverse drug reaction.

Depressed mood

Before taking the therapies, differences of SDS scores of the two groups were of no statistical significance (P=0.889); at the 12th week, SDS scores of the two groups prominently declined (P=0.000, P=0.005) and the observation group scored lower than the control group (P=0.008). At the 24th week, the observation group's scores went much lower than its pre-therapy data as well as that of the control group (both P=0.000). See **Table 4**.

Adverse drug reactions

ADR rates of the two groups were respectively 23.68% and 18.42%, difference of which was of no statistical significance (P=0.685). See **Table 5**. ADRs were relatively mild and obviously relieved after symptomatic treatment. Patients could continue their participation in the research.

Discussion

Western medicine treatment for cognitive and mental impairment caused by CSVD mainly depends on cholinesterase inhibitors and memantine. However, in an overall view, its effect on improving clinical symptoms and CSVD and patients' quality of life is limited. There are also some side effects [9]. In recent years, Chinese medicine's diagnostic philosophy of treatment based on syndrome differentiation, together with its small side effects, makes it a distinctly good option for treating vascular dementia.

MMSE and MoCA used in this study are internationally acknowledged cognitive function assessments and are the two that are mostly widely used in clinical application [10]. MMSE is appropriate for moderate patients while MoCA is more sensitive to test of mild cognitive impairment patients. Using both of the two can evaluate impairment more accurately. According to results of this study, at the 12th week, MMSE and MoCA scores of the two groups were obviously elevated compared with pre-therapy data (P=0.002, P=0.007, P=0.000, P=0.003). The observation group's scores went higher than the control group's (P=0.010, P=0.014). At the 24th week, those scores of the former group went much higher than that of the latter as well as that of themselves before taking the therapies (P=0.000, P=0.015, P=0.000, P=0.011). The results suggested that kidney tonifying granules were effective at improving CSVD patients' cognitive functions. CSVD falls in the scope of "Apoplexy" in Chinese medicine and cognitive dysfunction falls in "dementia". Cerebral small vessels are like "collaterals", the middle and lower structure of "meridian channels" in collateral disease theory in Chinese medicine. Collateral diseases are characterized by "easily cause stasis and obstruction", "easy to get in hard to get out" and "easy to form" which are like clinical symptoms of cognitive impairment caused by CSVD such as it's being hard to discover, long progression and hard to cure.

In Chinese medicine concept, cognitive impairment and vascular depression caused by CSVD have associations with blood stasis. If blood stasis happens in brain collateral channels, qi-blood circulation will be obstructed, organizations losing nourishments and brain activities

disabled [11]. Treatment by Chinese medicine always clings to the principle of dispersing blood stasis and dredging collaterals, together with the adoption of tonifying qi, clearing wind and detoxifying. Prescription in this study contains cistanche, lumbricus, and the root of red-rooted salvia, radix curcumae and bitter cardamom. Cistanche, as the monarch drug in this prescription, has the effect of nourishing essence and blood, tonifying kidney yang and essence and invigorating the brain. Its effective constituent, phenylethanoid glycosides, is a strong antioxidant [12]. Researches have proven that, phenylethanoid glycosides can remarkably improve cognitive function of vascular dementia patients, decrease dementia degree and improve patients' capability of managing daily life [13, 14]. The rest drugs of the prescription, (lumbricus, the root of red-rooted salvia, radix curcumae and bitter cardamom) are ministerial drugs. Lumbricus can disperse liver wind, clear and activate the channels and collaterals. The root of red-rooted salvia helps promoting blood circulation to remove blood stasis and accelerate tissue regeneration; bitter cardamom resolving phlegm, removing blood stasis and calming heart for resuscitation; radix curcumae promoting qi circulation, removing obstruction in the collateral and cooling blood and remove stasis. Modern researches show that lumbricus extractives help adjusting balance of prostacyclin and thromboxane and inhibiting production of endothelin, increasing plasma NO concentration, facilitating angiectasis and reducing blood resistance and increasing cerebral microcirculation blood flow [15]. The effective constituent of the root of red-rooted salvia, tanshinone-II, can boost generation of endothelial cells and dilation of blood vessels and induce angiogenesis; decrease expression of βamyloid peptide and thereby relieve damage of brain cells [16]. According to modern medical research findings, bitter cardamom is effective at protecting the neuron and could be used for treating Alzheimer Disease and other mental retardation. It has the effect of antioxidant, anti-aging, and reducing excitatory toxicity on neurocytes [17, 18].

At the 12th week of the therapy, the two groups' SDS score declined distinctly than their pre-therapy data (P=0.000, P=0.005) while the observation group's SDS score was even lower than the control group (P=0.008). At the 24th week, the observation group's SDS score went much lower than that of the control group as well as its pre-treatment value (both P=0.000). The results show that kidney tonifying granules are effective for relieving depression and improving quality of life. Modern pharmacological studies found out that radix curcumae has anti-depression effect [19]. Though its pathogenesis is not clear yet, it is related to inhibiting cerebral monoamine oxidase, raising amount of monamine transmitter like cerebral 5-hydroxytryptamine. All the drugs in this prescription coordinates complementarily and effectively to tonify kidney and spleen, nourish blood and essence, relieve uneasiness fundamentally and promote blood circulation to remove blood stasis and obstructions and mentally resuscitate palliatively. Reijmer et al. found out that vascular dementia patients, if take kidney tonifying granules, show obvious improvements on cognitive function [20]. The pathogenesis might be adjusting level of insulin-like growth factor-1, accelerating endothelial cells to release NO and bringing down endothelin-1 level, to enhance neuron metabolism and restore cognitive function. In this study, ADR rates of the observation group and control group were respectively 23.68% and 18.42%, difference of which was of no statistical significance (P=0.685). Since there's no withdrawal of treatment due to severe adverse drug reaction, the granules' clinical application is safe. The drawback is that the sample was small. If there's bigger sample and longer observation on cognitive function alterations after drug withdrawal like 18, 24 months even 3 years, the finding would be more significant.

In conclusion, kidney tonifying granules can help improve cognitive impairment and depression caused by CSVD. It is safe and worth wide clinical application.

Acknowledgements

This work was supported by Integrated Chinese and Western Medicine Project in Shanghai General Hospitals for the Clinical Study of Combination of Traditional Chinese and Western Medicine in the Treatment of Cerebral Small Vascular Disease (ZHYY-ZXYJHZX-2016).

Disclosure of conflict of interest

None.

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References

[1] Wei J, Zhang Y, Zhang HQ, Zhou LY and Dong T. Electrophysiological studies of treatment with reversible acetylcholinesterase inhibitor in cognitive impairment caused by cerebral small vessel disease. Chinese Journal of Neuroimmunology and Neurology 2016; 23: 34-37.

[2] Li HH. A study on the functional network of the cognitive dysfunction of cerebrovascular diseases with the help of chemical stasis tongluo drug. Guangzhou University of Chinese Medicine 2016.

[3] Wardlaw JW, Doubal FN, Valdes-Hernandez M, Wang X, Chappell FM, Shuler, Armitage PA, Carpenter TC, Dennis MS. Blood-brain barrier permeability and long-term clinical and imaging outcomes in cerebral small vessel disease. Stroke 2013; 44: 525-527.

[4] Ni CY and Wang F. Research progress of drug treatment of cerebral small vascular disease. Journal of Bengbu Medical College 2016; 41: 279-281.

[5] Xu J. The effect of oxiracetam on the cognitive function of vascular dementia rats and its role in PI3K/Akt signal transduction pathway. Guangzhou University of Chinese Medicine 2016.

[6] Issac TG, Chandra SR, Rajeswaran J, Christopher R and Philip M. Demographic features and neuropsychological correlates in a cohort of 200 patients with vascular cognitive decline due to cerebral small vessel disease. Indian J Psychol Med 2016; 38: 127-132.

[7] Zheng HW. Study on microglia cell polarization and white matter injury in hippocampal area of rats with vascular cognitive dysfunction. Study on microglia cell polarization and white matter injury in hippocampal area of rats with vascular cognitive dysfunction. The Second Military Medical University 2016.

[8] Varghese V, Chandra SR, Christopher R, Rajeswaran J, Prasad C, Subasree R and Issac TG. Factors determining cognitive dysfunction in cerebral small vessel disease. Indian J Psychol Med 2016; 38: 56-61.

[9] Shi YF. The clinical effect of nimodipine combined with ginkgo leaf in the treatment of cognitive dysfunction caused by cerebrovascular diseases. Modern Diagnosis & Treatment 2017; 28: 54-55.

[10] Ogata J, Yamanishi H and Ishibashi-Ueda H. Cerebral small vessel disease: the pathological features of cerebral amyloid angiopathy. Brain Nerve 2013; 65: 879-885.

[11] Craggs LJ, Hagel C and Kuhlenbaeumer G. Quantitative vascular pathology and phenotyping familial and sporadic cerebral small vessel diseases. Brain Pathol 2013; 23: 547-557.

[12] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge Rv, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB and Dichgans M. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013; 12: 822-838.

[13] Wang TS. Clinical study on the treatment of vascular dementia due to stagnation of blood stasis syndrome. Modern Journal of Integrated Traditional Chinese and Western Medicine 2016; 25: 316-317, 342.

[14] Ihara M. Management of cerebral small vessel disease for the diagnosis and treatment of dementia. Brain Nerve 2013; 65: 801-809.

[15] Han M and Han PX. The effect of donepezil combined with nimotop in the treatment of cognitive dysfunction caused by cerebrovascular diseases. Chinese Journal of Gerontology 2017; 37: 1125-1127.

[16] Jellinger KA. Pathology and pathogenesis of Vwular cognitive impairment-A critical update. Front Aging Neuresci 2013; 21: 17-19.

[17] Braun H and Schreiber S. Microbleeds in cerebral small vessel disease. Lancet Neurol 2013; 12: 735-736.

[18] Makin SD, Turpin S, Dennis MS and Wardlaw JM. Cognitive impairment after lacunar stroke: systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes. J Neural Neuresurg Psychiatry 2013; 84: 893-900.

[19] Esiri MM, Joachim C, Sloan C, Christie S, Agacinski G, Bridges LR, Wilcock GK and Smith AD. Cerebral subcortieal small vessel disease in subjects with pathologically confirmed Alzheimer Aisease: a clinicopathoiogic study in the Oxford project to investigate memory and ageing (OPTIMA). Alzheimer Dis Assoc Disord 2014; 28: 30-35.

[20] Reijmer YD, Leemans A, Caeyenberghs K, Heringa SM, Koek HL and Biessels GJ. Disruption of cerebral networks and cognitive impairment in Alzheimer Disease. Neurology 2013; 80: 1370-1377.