Effect of Pushen capsule for treating vascular mild cognitive impairment: a pilot observational study

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Abstract

Objective: Traditional Chinese medicine (TCM) may be beneficial for vascular dementia (VaD). We evaluated the efficacy of Pushen capsule, a compound containing several TCM components, for treating vascular mild cognitive impairment (VaMCI).

Methods: Seventy outpatients with VaMCI were randomized to Pushen capsule or control treatment with Ginkgo biloba. Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Subjective Memory Loss Rating Scale scores; and lipid, lipoprotein, and haemorheological parameters were collected at baseline, week 4, and week 12 of treatment.

Results: MMSE score at week 12 was significantly higher in the treatment group compared with baseline ($t = -2.352$) but was not significantly different from week 12 in the control group. The MoCA score at week 12 was higher than that at baseline for both the treatment and control groups ($t = -2.619$ and -2.582, respectively), as was the "delayed recall" item score. Subjective memory loss score and the cognitive function "forgetting acquaintance's name" were significantly higher in the treatment group at week 12 than at baseline ($t = -2.621$ and $\chi^2 = 4.419$, respectively). Lipid, lipoprotein, and haemorheological parameters were significantly different after treatment in both groups.

Conclusion: The benefits of Pushen capsule on cognitive function in VaMCI were comparable with that of Ginkgo biloba.

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Introduction

With increasing life expectancies, dementia has become a growing social health burden. According to a World Health Organization (WHO) 2019 report, 50 million people live with dementia globally.[1] In China, the number of people with dementia reached 9.19 million in 2010, and the prevalence ranged from 2.6% in people aged 65 to 69 years to 60.5% in people aged 95 to 99 years.[2] The dementia epidemic and the financial burden associated with family care costs remain two of the biggest challenges for global public health systems.

Vascular dementia (VaD), the second most common form of dementia following Alzheimer's disease (AD), accounts for at least 25% of cases of dementia.[1] VaD has been accepted as the latest stage of vascular cognitive impairment (VCI), which refers to all forms of cognitive deficits related to cerebrovascular disease or relevant risk factors. Incidence rates of VaD are age related, with the prevalence doubling every 5.3 years.[3] Stroke is the most common cause of VaD, with 10% of patients with first stroke living with VaD and more than one third of recurring stroke cases accompanied by VaD.[4] Multiple efforts to investigate treatment options for VaD have been made in recent decades, including clinical trials of cholinesterase inhibitors and nonpharmacological treatments; however, valid therapies to prevent the associated progressive cognitive and functional decline are not yet available.[5]

In contrast to the irreversible progression of VaD, vascular mild cognitive impairment (VaMCI) can be considered a stage of VCI in which intervention is feasible. VaMCI is the early stage of VCI between normal ageing and VaD, in which the severity of cognitive decline does not meet the criteria for dementia.[6] VaMCI can be considered an overlap of VCI with mild cognitive impairment (MCI).

The prevalence of VaMCI is estimated to be twice that of VaD.[7] Moreover, just as MCI is likely to progress to AD, VaMCI is the greatest risk factor for VaD.[8] Hence, effective treatment of VaMCI may protect patients from developing VaD, thus decreasing its incidence.

Previous studies have indicated that traditional Chinese medicine (TCM) is effective in the treatment of VaD by regulating cerebral circulation and cellular metabolism.[9] Ginkgo biloba is widely used in China to improve the symptoms of cerebral ischaemia because of its antioxidative and protective effects on neuronal cells.[10,11] Existing evidence suggests that Ginkgo biloba extract (EGb 761) can enhance the integrity of the cerebral microvasculature and strengthen the ability of cerebral microvascular endothelial cells to resist damage resulting from hypoxia, hyperglycaemia, and amyloid-beta (Aβ) protein.[12,13] Additionally, various clinical trials have reported the efficiency of EGb 761 in ameliorating mild-to-moderate age-related cognitive impairments induced by AD, VaD, and mixed dementia.[14–16] Furthermore, EGb 761 has been shown to improve the cognitive performance of patients with MCI, including those with VaMCI.[17–19]

Pushen capsule is a compound preparation of various TCM drugs, and primarily consists of Polygonum multiflorum, Pollen Typhae, Salvia miltiorrhiza, Ligusticum chuanxiong, and paeoniflorin. Several registered pharmaceutical products containing Salvia miltiorrhiza extracts, such as Danshen dripping pill and water-soluble Danshensu, are widely used in clinical settings in China and produce effects that are beneficial to the cardiovascular system including microcirculation improvement, protection against myocardial ischaemia/reperfusion injury, and antiplatelet aggregation.[20,21] Polygonum multiflorum and Ligusticum chuanxiong have been reported

to improve clinical cognitive impairments induced by occlusion of cerebral blood flow.[22,23] Recently, Pushen capsule was reported by the China Food and Drug Administration to regulate hyperlipemia, a risk factor for cognitive impairment, in China.[24] However, the efficacy of Pushen capsule for the treatment of VaMCI has not yet been investigated.

In the present study, we evaluated the clinical efficacy of Pushen capsule for treating VaMCI and compared it with that of Ginkgo biloba. Furthermore, blood serum lipid, lipoprotein, and hemorheological parameters of patients with VaMCI were investigated.

Methods

Trial design and population

A randomized hospital-based study with blinded outcome evaluation was performed. Seventy patients with VaMCI were enrolled from the outpatient neurology department at Zhongda Hospital affiliated with Southeast University between April 2016 and April 2018. The groups were assigned randomly to one of two groups as follows: patients labelled with even numbers were given Pushen capsule for 12 weeks and those with an odd number were assigned to the control group and given Ginkgo biloba for 12 weeks. Neither the participants nor the administering clinicians were blinded to the intervention. Written informed consent, which clarified the uncertainty effect of the cognitive improvement and the probable adverse effects of both interventions, was obtained from each participant. The research was conducted according to the World Medical Association Declaration of Helsinki. This experimental protocol was approved by the Ethics Committee of Nanjing University of Chinese Medicine and Southeast University (approval number: 2013NL-026-02). The diagnosis of VaMCI was based on

the criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which was updated by the American Psychiatric Association (APA) in 2013, while referencing the statement from the American Heart Association/American Stroke Association.[3] Patients were eligible for inclusion in the trial if they were 18 years of age or older, presented with subjective cognitive impairment that interfered in the performance of activities instrumental for daily living, and met the criteria for MCI with cognitive testing.[25] In addition, patients were required to have an Mini Mental State Examination (MMSE) score >24 and Montreal Cognitive Assessment (MoCA) score >22 to be diagnosed with MCI and not VaD. We limited the enrolment to patients who had been diagnosed with stroke or lacunar infarction at least 6 months prior to enrolment to reduce the effects of confounding factors and time bias. Ischaemic stroke was diagnosed as an acute focal neurological deficit lasting more than 24 hours and an infarct lesion with a high hyper-intense signal on diffusion-weighted magnetic resonance imaging (MRI). Haemorrhagic stroke was confirmed as a new lesion with a high hyperintense signal on a brain computed tomography (CT) scan. For included patients, cognitive impairment should follow stroke. Patients were excluded if they had depression or other mental disorders, traumatic brain injuries, epilepsy, encephalitis, Parkinson's disease, tumour, hypothyroidism, severe anaemia, infections, or other endocrine diseases. Patients were also excluded if there was a clear contraindication for either Pushen capsule or Ginkgo biloba.

Interventions

Patients who were assessed as having VaMCI in the treatment group were orally administered Pushen capsule from Jiangsu Suzhong Haixin Pharmaceutical Company (Jiangsu Sheng, China) at a dose of 1.8 mg,

three times a day without any change in other treatment. In the control group, patients were orally administered Ginkgo biloba tablets from the Yangtze River Pharmaceutical Group (Taizhou, China) at a dose of 19.2 mg, three times a day. Patients were asked to adhere to the assigned treatment for 12 weeks unless an adverse reaction was experienced.

Cognitive function assessment

Using an assessment scale approach, we performed a primary analysis to exclude the effect of depression and anxiety using the Hamilton Depression Scale (HAMD-17) and Hamilton Anxiety Scale (HAMA). The MMSE and MoCA were used to assess cognitive function at baseline and at weeks 3 and 12 of treatment. A previous study showed that a short memory questionnaire was useful when screening for MCI.[26] We further expanded on the memory questions, resulting in the Subjective Memory Loss Rating Scale (Box 1) to detect the effect of treatment by assessing answers to specific questions targeting problems often encountered in daily life.[4,27]

Data collection

Demographic data were collected at the first assessment (baseline), while clinical data, including the MRI brain scan and the MMSE, MoCA, and Subjective Memory Loss Rating Scale scores, were recorded at all three time points (baseline, week 4, and week 12). Levels of fasting blood lipids and lipoproteins including triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apoA1, apoB, and lipoprotein α, as well as haemorheological parameters consisting of blood viscosity at high, medium, and low shear rate; capillary plasma viscosity; and haematocrit were recorded. Follow-up data were collected at week 3 and week 12 of treatment. To detect adverse effects, items reflecting liver and kidney function and creatine kinase were examined. The statisticians who analysed the data were blinded to the intervention.

Statistical analysis

We estimated that at least 35 patients with VaMCI would need to be assigned to each treatment group. This calculation was based on conservative estimates of a 15%

Box 1. Supplementary Subjective Memory Loss Rating Scale.

Q1: If the score of your best memory state is ten, how many points do you give to your current memory?
(The maximal score is ten, and the answer score should be the range from zero to ten in integers.)

Q2: Which of the following aspects of memory do you experience?
(The answer could be more than one)
1. I can't remember the name of someone who was familiar to me before.
2. I forget what I want to do when I arrive at a place or enter a room.
3. I forget where I have put the thing I was holding, such as keys or wallet.
4. I always leave something behind when I leave a place.
5. I lose my way sometimes in familiar surroundings
6. I can't remember what I have read in newspaper or the content of the TV just now.
7. I can't find the right word to express my ideas when talking with others.
8. I can't recall what someone told me or what I did a few days ago.
9. I can't remember the phone number that I dialled.

participant dropout rate. All quantitative data are presented as the mean ± standard deviation. For data of equal variance and normal distribution, statistical comparisons between groups were performed using Student's t-test for between-group comparisons or one- or two-way analysis of variance (ANOVA) for comparisons among the three time points. Dunnett's t-test was used for multiple comparisons. Categorical data are shown as percentages and were assessed using the chi-squared test. Data that failed tests for normality and equal variance were assessed using a non-parametric test. All reported P values are two-sided, and no adjustment was made for multiple comparisons. All analyses were performed using SPSS software, version 19 (IBM Corp., Armonk, NY, USA) at an alpha level of 0.05.

Results

Characteristics of the study population

From 1 April 2016, to 28 April 2018, 70 patients were screened and 62 eligible patients were randomly assigned to Pushen capsule (n = 30) and or to the control group treated with Ginkgo biloba tablets (n = 32). The loss-to-follow-up rate at week 12 was 11%, resulting from a loss of contact and hospitalization. The baseline characteristics of patients are summarized in Table 1. There was no difference in baseline scores of the scales between the two groups. No significant differences were found in the distribution of demographics, medical history, or laboratory data at baseline, apart from HDL, apoA1, and haematocrit values.

Effect on cognitive function

The MMSE and MoCA were used to investigate the effect of Pushen capsule and Ginkgo biloba tablets on cognitive function, in addition to the Subjective Memory Loss Rating Scale. Compared with the MMSE score at baseline, the mean MMSE score for the treatment group was significantly improved at week 12 after treatment with Pushen capsule ($t = -2.352$, $P = 0.022$) but was not significantly different from the MMSE score in the control group at the same time point ($t = -1.913$) (Figure 1a). Specific items of the MMSE were also studied in the two groups, but the scores for these specific items did not change after treatment (Table 4). Furthermore, there were no significant differences between the two groups when comparing the scores at week 0 and week 12.

The mean MoCA score at the first assessment was 24.76 ± 2.95 and 24.07 ± 3.13 in the treatment group and control group, respectively, and were lower than the MMSE scores, which were 27.38 ± 2.04 and 27.86 ± 1.96, respectively. Our results were consistent with those from a previous study, which showed that MoCA is a concise cognitive screening tool with high sensitivity and specificity for detecting MCI in patients performing in the normal range on the MMSE.[28,29] Although the score in week 4 was not significantly different from baseline in both the treatment and control groups ($t = -1.539$ and -1.500, respectively), it was higher in week 12 ($t = -2.619$ and -2.582; $P = 0.011$ and 0.013, respectively) (Figure 1b), and the score of the "delayed recall" item increased significantly with treatment ($P = 0.018$ and 0.026, respectively) (Table 2). Interestingly, although neither group showed improvements in the "Visuospatial/executive function" score over time, the control group performed better than the treatment group on this item ($Z = -3.649$, $P = 0.00$) (Table 2).

We have experienced that post-stroke patients frequently complain of hypomnesis in clinical practice. Hence, we further explored the subjective memory loss that may occur in daily life. In the treatment group, the score on the Subjective Memory

Table 1. Baseline characteristics of patients with vascular mild cognitive impairment.

	Treatment group (n=30)	Control group (n=32)	t or χ^2 value*	P value
Age, years	64.07 ± 9.18	65.71 ± 8.21	0.507	0.479
Male sex, no. (%)	15 (50.0)	20 (62.5)	0.984	0.321
Educational background, no. (%)			0.946	0.623
Illiteracy	1 (3.3)	2 (6.3)		
Primary education	5 (16.7)	3 (9.4)		
Secondary education or above	24 (80.0)	27 (84.4)		
Body mass index	23.86 ± 3.33	24.35 ± 2.77	0.372	0.544
Medical history, no. (%)				
Tobacco use	10 (33.3)	14 (43.8)	3.050	0.218
Alcohol use	19 (63.3)	19 (59.4)	1.938	0.380
Hypertension	12 (40.0)	17 (53.1)	3.600	0.165
Atrial fibrillation	2 (6.7)	3 (9.4)	2.156	0.340
Diabetes mellitus	8 (26.7)	15 (46.9)	5.396	0.067
Other disease	20 (66.7)	23 (71.9)	0.198	0.657
Genetic history	1 (3.3)	1 (3.1)	0.002	0.963
Stroke, no. (%)			1.552	0.213
Lacunar infarction	15 (50.0)	21 (65.6)		
Other type	15 (50.0)	11 (34.4)		
Lipids and lipoprotein				
TC (mmol/L)	5.02 ± 1.44	4.93 ± 1.09	0.263	0.794
TG (mmol/L)	1.46 ± 1.04	1.73 ± 0.90	−1.027	0.309
HDL-C (mmol/L)	1.25 ± 0.35	1.06 ± 0.17	2.519	0.015
LDL-C (mmol/L)	2.96 ± 1.05	3.06 ± 0.82	−0.404	0.688
apoA1 (g/L)	1.32 ± 0.45	1.10 ± 0.23	2.331	0.023
apoB (g/L)	0.86 ± 0.26	0.84 ± 0.23	−0.583	0.562
Lipoprotein-α (mg/L)	336.69 ± 209.65	294.75 ± 222.1	0.733	0.467
Blood viscosity				
High shear rate§	4.56 ± 0.43	4.60 ± 0.58	−0.244	0.808
Medium shear rate§	5.13 ± 0.47	5.12 ± 0.60	0.082	0.935
Low shear rate§	8.88 ± 1.04	9.31 ± 1.38	−1.352	0.182
Capillary plasma viscosity	1.27 ± 0.12	1.25 ± 0.10	0.710	0.481
Haematocrit (%)	43.03 ± 3.64	45.20 ± 4.35	−2.053	0.045
Median HAMD-17 score (IQR[†])	2 (0–4)	0.5 (0–3.75)	0.534	0.596
Median HAMA score (IQR[†])	3 (2–4.5)	2 (0–3.75)	1.971	0.054
Cognitive function				
MMSE score	27.38 ± 2.04	27.86 ± 1.96	−0.901	0.371
MoCA score	24.76 ± 2.95	24.07 ± 3.13	0.854	0.397
Subjective memory loss Rating scale score	6.17 ± 1.73	6.43 ± 1.48	−0.600	0.551

TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; HAMD-17, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment.

Note: *t or χ^2 value: Student's t-test was used to compare quantitative data, including age, body mass index, lipids and lipoprotein, blood viscosity, and HAMD-17 and HAMA scores, while other categorical data were compared by chi-squared test,

§Units of blood viscosity at high, medium, and low shear rates are (mPa.s)|150(1/s), (mPa.s)|60(1/s), and (mPa.s)|10(1/s).
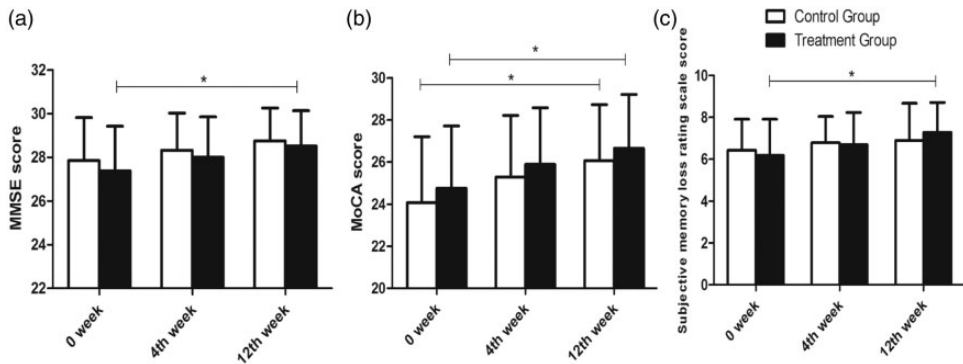
†IQR denotes interquartile range.

Figure 1. Effect of Pushen capsule and Ginkgo biloba tablets on cognitive function as assessed by MMSE (a), MoCA (b), and Subjective Memory Loss Rating Scale (c).

Table 2. Scores for specific items of the Montreal Cognitive Assessment in treatment and control groups ($x \pm s$).

	Treatment group			Control group			t or Z value*	P value*
	Week 0	Week 4	Week 12	Week 0	Week 4	Week 12		
Visuospatial/ executive function	4.38 ± 0.73	4.48 ± 0.79	4.55 ± 0.69	4.11 ± 0.99	4.50 ± 0.75	4.61 ± 0.63	−3.649[#]	0.000[#]
Naming	2.97 ± 0.19	3.00 ± 0.00	3.00 ± 0.00	2.96 ± 0.19	2.96 ± 0.19	3.00 ± 0.00	−0.025	0.980
Attention	5.45 ± 1.15	5.55 ± 1.09	5.59 ± 0.98	5.64 ± 0.68	5.64 ± 0.73	5.61 ± 0.74	1.380	0.173
Language	2.17 ± 0.66	2.28 ± 0.65	2.31 ± 0.71	2.07 ± 0.77	2.29 ± 0.76	2.32 ± 0.82	−0.631	0.531
Abstraction	1.03 ± 0.82	1.28 ± 0.75	1.48 ± 0.63	1.32 ± 0.82	1.36 ± 0.73	1.46 ± 0.69	1.884	0.065
Delayed recall	2.34 ± 1.68	2.97 ± 1.48	3.38 ± 1.29[¥]	1.82 ± 1.63	2.36 ± 1.34	2.79 ± 1.32[¥]	0.263	0.794
Orientation	5.93 ± 0.26	5.93 ± 0.26	5.93 ± 0.26	5.89 ± 0.42	5.93 ± 0.26	6.00 ± 0.00	−1.160	0.251

Note: *t value and P value were calculated by t-test comparing the score at week 0 and week 12 between the two groups.
[#]Wilcoxon signed rank test used to calculate the Z value by comparing the score for visuospatial/executive function in week 0 with week 12 because of the heterogeneity of variance.
[¥]Score compared with that at week 0 by t-test, resulting in P < 0.05.

Loss Rating Scale was significantly improved at week 12 ($t = -2.621$, $P = 0.011$) (Figure 1c). In contrast, the score in the control group remained unchanged with treatment ($t = -1.066$). Half of the participants reported that they could not remember where they had placed an important item such as their wallet or keys in daily life (Table 3). In our study, Pushen capsule did not ameliorate this impairment but did have a positive effect on the score for "forgetting acquaintance's name" ($\chi^2 = 4.419$, $P = 0.036$). The treatment group performed better than the control group for this item ($\chi^2 = 6.257$, $P = 0.044$) (Table 3).

Effect on blood lipids and lipoproteins

Given the reported efficacy of Pushen capsule in improving hyperlipaemia,[24] we examined the changes in blood lipids and lipoproteins in the two groups. TC and

Table 3. Scores for specific items of Subjective Memory Loss Rating Scale in treatment and control groups (no. [%]).

Item forgotten	Treatment group			Control group			χ^2 value*	P value*
	Week 0	Week 4	Week 12	Week 0	Week 4	Week 12		
Acquaintance's name	18 (62.1%)	9 (31.0%)	10 (34.5%)¥	15 (53.6%)	17 (60.7%)	16 (57.1%)	6.257	0.044
What I want to do	17 (58.6%)	14 (48.3%)	14 (48.3%)	12 (42.9%)	13 (46.4%)	9 (32.1%)	0.004	0.998
Where the key/wallet is	20 (69.0%)	19 (65.5%)	17 (58.6%)	16 (57.1%)	14 (50.0%)	15 (53.6%)	2.167	0.338
Leave something behind	8 (27.6%)	10 (34.5%)	8 (27.6%)	4 (14.3%)	8 (28.6%)	6 (21.4%)	2.126	0.345
Lost the way	3 (10.3%)	2 (6.9%)	2 (6.9%)	2 (7.1%)	0 (0%)	1 (3.6%)	1.486	0.476
What I have read just now	17 (58.6%)	12 (41.4%)	10 (34.5%)	16 (57.1%)	10 (35.7%)	11 (39.3%)	1.083	0.582
Expressing an idea	10 (34.5%)	4 (13.8%)	4 (13.8%)	11 (39.3%)	8 (28.6%)	5 (17.9%)	2.879	0.237
Recalling what happened	8 (27.6%)	7 (24.1%)	7 (24.1%)	10 (35.7%)	12 (42.9%)	5 (17.9%)	1.221	0.543
Phone number	5 (17.2%)	3 (10.3%)	3 (10.3%)	7 (25.0%)	3 (10.7%)	4 (14.3%)	1.164	0.559

Note: *χ^2 value and P value were calculated by the chi-squared test compared with week 0 and week 12 between the two groups.
¥Values compared with week 0 in the chi-squared test, resulting in $P < 0.05$.

Table 4. Score on specific items of MMSE in treatment and control groups (x ± s).

	Treatment group			Control group			t value*	P value*
	Week 0	Week 4	Week 12	Week 0	Week 4	Week 12		
Orientation	9.66 ± 0.61	9.83 ± 0.47	9.86 ± 0.44	9.64 ± 0.73	9.71 ± 0.60	9.93 ± 0.26	−0.513	0.610
Registration	2.86 ± 0.44	2.93 ± 0.26	3.00 ± 0.00	2.93 ± 0.26	3.00 ± 0.00	3.00 ± 0.00	0.689	0.494
Attention and calculation	4.10 ± 1.14	4.28 ± 1.03	4.38 ± 0.90	4.43 ± 0.84	4.50 ± 0.79	4.61 ± 0.79	0.683	0.498
recall	1.79 ± 1.05	2.00 ± 0.76	2.31 ± 0.89	2.04 ± 0.88	2.21 ± 0.88	2.32 ± 0.77	1.297	0.200
Language and praxis	8.97 ± 0.19	8.97 ± 0.19	8.97 ± 0.19	8.82 ± 0.55	8.89 ± 0.42	8.89 ± 0.42	−1.467	0.148

Note: *t value and P value were calculated by t-test comparing the score in week 0 and week 12 between the two groups.

LDL-C levels in the treatment group differed among the three time points tested ($F = 6.126$ and 3.976; $P = 0.003$ and 0.022, respectively). Compared with the levels at baseline, the TC and LDL-C levels were lower at week 12 ($P = 0.001$ and 0.012, respectively) (Table 5). However, only the TC level in the control group differed among the three time points ($F = 3.369$; $P = 0.039$), and further comparison showed that Ginkgo biloba tablets reduced the TC level at week 12 ($P = 0.023$) (Table 5).

Effect on haemorheology

In both the treatment and control groups, blood viscosity at low, medium, and high shear rates was significantly different among the three time points tested ($F = 6.311$, 6.078, and 4.489; and 4.158, 6.051, and 3.566, respectively; $P = 0.003$, 0.003, and 0.014; and 0.019, 0.004, and 0.033, respectively). In comparison with blood viscosity at week 0, blood viscosity at low, medium, and high shear rates in both groups was significantly lower at week 12 ($P = 0.001$, 0.002, 0.007 in the treatment group and 0.014, 0.002, and 0.017 in the control group, respectively). Notably, Ginkgo biloba tablets effectively improved haematocrit ($F = 6.71$, $P = 0.02$), which was reduced to 41.77 ± 3.53 at week 12 compared with 45.20 ± 4.35 at baseline ($P = 0.02$) (Table 6).

Table 5. Blood lipids and lipoproteins in treatment and control groups.

	Treatment group			Control group				
	Week 0	Week 4	Week 12	Week 0	Week 4	Week 12	t value*	P value*
TC (mmol/L)	5.02 ± 1.44	4.43 ± 1.02	3.92 ± 1.07*	4.93 ± 1.09	4.45 ± 1.17	4.16 ± 1.08*	0.963	0.340
TG (mmol/L)	1.46 ± 1.04	1.19 ± 0.68	1.28 ± 0.88	1.73 ± 0.90	1.48 ± 0.84	1.29 ± 0.50	1.713	0.092
HDL-C (mmol/L)	1.25 ± 0.35	1.31 ± 0.27	1.35 ± 0.44	1.06 ± 0.17	1.13 ± 0.21	1.16 ± 0.22	0.461	0.647
LDL-C (mmol/L)	2.96 ± 1.05	2.65 ± 0.87	2.26 ± 0.91*	3.06 ± 0.82	2.74 ± 0.96	2.52 ± 0.87	0.589	0.558
apoA1 (g/L)	1.32 ± 0.45	1.31 ± 0.34	1.26 ± 0.41	1.10 ± 0.23	1.11 ± 0.23	1.14 ± 0.21	0.412	0.682
ApoB (g/L)	0.86 ± 0.26	0.86 ± 0.33	0.72 ± 0.26	0.90 ± 0.23	0.84 ± 0.23	0.78 ± 0.22	1.071	0.289
Lipoprotein α (mg/L)	336.69 ± 209.65	326.28 ± 218.64	301.97 ± 201.61	294.75 ± 222.17	326.64 ± 229.05	288.57 ± 228.09	−0.385	0.702

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Note: *t value and P value were calculated by t-test comparing the score in week 0 and week 12 between the two groups.
*Score compared with that at week 0 in ANOVA, resulting in $P < 0.05$.

Table 6. Hemorheological parameters in the treatment and control groups.

	Treatment group			Control group				
Blood viscosity at	Week 0	Week 4	Week 12	Week 0	Week 4	Week 12	t value*	P value*
Low shear rate	8.88 ± 1.04	8.38 ± 0.99	7.96 ± 0.95*	9.31 ± 1.38	8.56 ± 1.42	8.35 ± 1.07*	−0.648	0.520
Medium shear rate	5.13 ± 0.47	4.93 ± 0.48	4.70 ± 0.47*	5.12 ± 0.60	4.80 ± 0.54	4.60 ± 0.56*	1.293	0.202
High shear rate	4.56 ± 0.43	4.39 ± 0.44	4.21 ± 0.48*	4.60 ± 0.58	4.36 ± 0.63	4.15 ± 0.65*	1.522	0.134
Capillary plasma viscosity	1.27 ± 0.12	1.29 ± 0.13	1.25 ± 0.11	1.25 ± 0.10	1.25 ± 0.11	1.24 ± 0.12	1.017	0.314
Haematocrit (%)	43.03 ± 3.64	42.47 ± 3.86	42.33 ± 3.17	45.20 ± 4.35	42.14 ± 3.62	41.77 ± 3.53*	2.893	0.005

Note: Units of blood viscosity at low, medium, and high shear rate are (mPa.s)|10(1/s), (mPa.s)|60(1/s), and (mPa.s)|150(1/s).
*t value and P value were calculated by t-test comparing the score in week 0 and week 12 between the two groups.
*Score compared with that at week 0 in ANOVA, resulting in $P < 0.05$.

Adverse effects

The items reflecting liver and kidney function and creatine kinase function were all normal in both groups throughout the trial. In the treatment group, three participants complained of mild nausea on the days 12, 14, and 38. However, all three participants agreed to continue with study treatment.

Discussion

The present study focused on the effect of a TCM preparation in improving cognitive impairment, using Ginkgo biloba, the effects of which have been studied widely in recent years, as a positive control. Our results indicate that Pushen capsule improved cognitive function in patients with VaMCI, as demonstrated by increases in MMSE and MoCA scores as well as improvements in the "delayed recall" item. In addition, Pushen capsule ameliorated daily amnesia among patients, especially with respect to the item "forgetting acquaintance's name", whereas Ginkgo biloba did not have an effect on this item. These results suggest that Pushen capsule may represent a novel agent for the treatment of VaMCI.

A previous study reported that the MoCA is superior to the MMSE in discriminating between individuals with MCI and normal cognitive function.[30] In our study, Ginkgo biloba tablets had little effect on the MMSE score but improved the MoCA score, consistent with previous results.[30] Impaired function exhibited by impairments in the "delayed recalled" item occurs at a high rate in VaMCI patients, and our study indicated that Pushen capsule enhanced this item to a greater extent than it did other cognitive functions, which was in line with the effect of Pushen capsule on the item "forgetting acquaintance's name" when examining subjective memory loss encountered in daily life.

Multiple risk factors for cerebrovascular disease can lead to abnormal vascular endothelial structure and function, resulting in disordered blood haemorheology and subsequent activation of inflammation and oxidative stress, giving rise to advanced destruction of neurological as well as cognitive function. Lipid metabolism disorders and increased blood viscosity are also important in VCI[6] and can accelerate the formation of atherosclerosis and thrombosis and promote the transformation of VaMCI into VaD. Our results showed that Pushen capsule treatment reduced the levels of TC and LDL in addition to reducing blood viscosity. Furthermore, Ginkgo biloba decreased the level of haematocrit. Whether Pushen capsule and Ginkgo biloba affect cognitive function by improving lipid metabolism and blood viscosity requires further study.

Pushen capsule consists of various components of TCM including Polygonum multiflorum, which has been shown to enhance the activity of cyclooxygenase and the fluidity of the mitochondrial membrane in the hippocampus of AD rats.[31] Moreover, Salvia miltiorrhiza has been shown to reduce the deposition of Aβ by inhibiting BACE1 activity.[32] In addition, a herbal extracts of Salvia miltiorrhiza (tanshinone IIA) has been demonstrated to improve memory impairment in a chronic cerebral ischaemia rat model by regulating the levels of glutamate and γ-aminobutyric acid (GABA) and protecting against free radical insults.[33] However, the mechanism by which Pushen capsule might improve cognitive function has not been investigated to date. Similar to studies on the molecular mechanism of Ginkgo (EGb 761),[12,13] our group is currently exploring the molecular mechanism of Pushen capsule using cell and animal experiments. We aim to identify proteins regulated by Pushen capsule and the precise mechanism by which it exerts its effects in future studies.

Cholinesterase inhibitors[34] such as done-pezil hydrochloride play an important role in rapidly improving cognitive function, while TCM can exert its effects in cells or organs over prolonged periods.[9] The combination of cholinesterase inhibitors and TCM may potentially result in a synergistic effect on cognitive function. Furthermore, non-pharmacological treatments for VaMCI, such as acupuncture,[35,36] may be beneficial and cost-effective when combined with Pushen capsule treatment. Further studies are needed to explore these treatment strategies.

VaMCI, a preliminary stage of VaD, is caused by small vessel disease and the accumulation of lacunar infarcts and white matter changes that are responsible for the gradual progression of cognitive impairment.[37] Previous studies have indicated that VaMCI can be accompanied by other diseases, such as autoimmune disorders and depression, and that cognitive insult can be resolved by treating these disorders with or without specific treatment for VaMCI.[7,38] Moreover, some studies have shown that VaMCI is common among patients with stroke, and improves with stroke recovery.[39] Although our study was conducted in patients with MRI-confirmed stroke and showed that Pushen capsule and Ginkgo biloba could improve cognitive function, we cannot exclude the possibility of self-healing as not all cases of VaMCI progress to VaD.

This study had some limitations. Pushen capsule showed a beneficial effect in the treatment of VaMCI and improved blood lipid lipoprotein levels and haemorheological parameters. However, the validity of the results may have been affected by the small sample size, open-label study design, short follow-up time, and potential drug–drug interactions. Notably, the blood lipid and lipoprotein levels and haemorheological parameters of participants remained in the normal range throughout the study, despite showing significant changes over the treatment period. The effect of both types of TCM on hyperlipaemia and haemorheologic disorder requires further exploration. Furthermore, the beneficial treatment effects observed in the present study may be attributable to a slowing of functional decline rather than prevention of progression to VaD.[40] Therefore, further studies to evaluate the long-term efficacy of Pushen capsule and Ginkgo extract are required.

Conclusion

Our findings indicate that Pushen capsule may exert beneficial effects, comparable to those of Ginkgo biloba, on the cognitive function of patients with VaMCI, particularly the function of "delayed recall" assessed by the MoCA and the subjective cognitive function of "forgetting acquaintance's name". Moreover, risk factors for cerebrovascular disease such as lipid and lipoprotein levels and haemorheological parameters were significantly reduced following treatment with Pushen capsule and Ginkgo biloba.

Abbreviations

VaD: vascular dementia, AD: Alzheimer's disease, VCI: vascular cognitive impairment, VaMCI: vascular mild cognitive impairment, MCI: mild cognitive impairment, TCM: traditional Chinese medicine, Aβ: amyloid-beta, HAMD-17: Hamilton Depression Scale, HAMA: Hamilton Anxiety Scale, MMSE: Mini Mental State Examination, MoCA: Montreal Cognitive Assessment, TG: triglyceride, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, GABA: γ-aminobutyric acid

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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