Effect of reinforcing kidney-essence, removing phlegm, and promoting mental therapy on treating Alzheimer's disease

Ping Liu, Mingwang Kong, Songlin Liu, Gang Chen, Ping Wang

Abstract

OBJECTIVE: To explore the mechanism of reinforcing kidney-essence, removing phlegm, and promoting mental therapy in treating Alzheimer's disease (AD).

METHODS: Sixty patients with AD in Wuhan No.1 Hospital of Traditional Chinese Medicine for Geriatrics from May 2009 to April 2011 were randomly divided into two groups, with 30 in each group. Patients in Bushenhuatanyizhi group (BHY group) took BHY instant granules (6 g, twice per day). Patients in the control group took piracetam (0.8 g, 3 times per day). There were twelve weeks in a course. Changes in the mini-mental state examination (MMSE) score and Activity of Daily Living Scale (ADL) score were analyzed before and after treatment.

RESULTS: MMSE scores in the two groups increased and ADL scores decreased after treatment, compared with those before treatment (both \( P < 0.05 \)). The total effective rate was 86.67% in the BHY group (10 very effective, 13 effective, 7 non-responsive). The control group was 57.69% (5 very effective, 9 effective, 9 non-responsive) (\( P < 0.05 \)). Superoxide dismutase levels were increased, lipid peroxide and triglyceride levels decreased after treatment in the BHY group as compared with the control group.

CONCLUSION: Reinforcing kidney-essence, removing phlegm, and promoting mental therapy can improve cognitive function and daily life of AD patients. The mechanism of the therapy might be related to improving blood fat, scavenging free radicals, and inhibiting lipid peroxides.

INTRODUCTION

Alzheimer's disease (AD), characterized by progressive deterioration in cognition, function, and behavior, places a considerable burden on society. According to recent surveys, it is the sixth leading cause of all deaths and the fifth leading cause of death in persons aged ≥ 65 years. An estimated 35.6 million people currently suffer from AD worldwide. Moreover, it is predicted that AD will affect 1 in 85 persons globally by 2050. Currently, cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists are first-line pharmacotherapy in treating mild-to-moderate AD. However, they cannot prevent the condition of patients...
from deteriorating. As of 2012, more than 1000 clinical trials have been or are being conducted to find ways to treat AD. Therefore, finding an effective method to treat AD still poses a significant clinical challenge.6,7

Traditional Chinese Medicine (TCM) has a long history of preventing and treating cognitive decline.6,8 Although AD is a modern disease entity that has no direct analogue in the ancient Chinese medicine literature, disorders of memory and cognitive deficit are referred to as dementia throughout the classical literature. For example, in Sheng Nong Ben Cao Jing, the earliest pharmacopeia on materia medica in China, some TCM ingredients such as Yuanzhi (Radix Paeoniae), Renshen (Radix Ginseng), Huanglian (Rhizoma Coptidis), and Longyanrou (Arillus Longan) were recorded to ameliorate memory loss.9 Jing Yue Quan Shu contains the earliest known description of herbal therapeutic strategy for dementia.10 In Bian Zheng Lu, Shiduo Chen proposed that “treating phlegm is treating dementia”. Shiduo Chen also suggested that tonifying the spleen and stomach, resolving phlegm, and clearing the orifices of the heart are important in the treatment of dementia. A formula named Suxin Tang was developed for dementia. Suxin Tang is composed of Renshen (Radix Ginseng), Fuling (Porzia), Banxia (Rhiza Sassafras), Chaiku (Radix Bupleuri Chinensis), Huanglian (Rhizoma Coptidis), Wuizhyu (Fructus Evodiae Rutaceae), Zhizi (Fructus Gardeniae), Fuji (Fructus Aconiti Lateralis Preparata), Danggui (Radix Paeoniae Albae), and Sanzaoren (Semen Ziziphi Spinosae).11 Many Chinese herbal medicines including Shichangpu (Rhizoma Acori Tatarinowii), Yuanzhi (Radix Paeoniae), Renshen (Radix Ginseng), Canggu (Rhizoma Atractylodis Lanceae), Gancia (Radix Glycyrrhizae), Banxa (Rhiza Sassafras), Jianghuang (Rhizoma Curcumae Longae), Di huang (Radix Rehmannia), Gouquizi (Fructus Lycii), Roucongrong (Herba Cistanches Deserticolae), Shanyao (Rhizoma Dioscoreae Oppositae), and Fuling (Porzia) are used in senile dementia for memory and cognitive function improvement. In TCM, the AD clinical treatment take “reinforcing deficiency and improving intelligence” and “supplement deficiency without persisting pathogen” as the basic principle of treatment. Clinical practice showed that replenishing kidney-essence, removing phlegm and promoting mentality therapy is an effective method to treat AD. Experimental studies has demonstrated that this therapy is effective in the treatment of mild cognitive impairment, and early and moderate Alzheimer’s disease.12,13 Bushenhuatanyizhi instant granules is the main prescription for the therapy for AD. Therefore, we conducted a clinical study to investigate effect of reinforcing kidney-essence, resolving phlegm, and promoting mental therapy in treating Alzheimer’s disease.

MATERIALS AND METHODS

Participants
Overall, 60 AD patients were selected from Wuhan No.1 Hospital of TCM for Geriatrics from May 2009 to April 2011. Patients were included if, referring to the diagnostic criteria of the DSM-IV on AD and consulting the possible AD criteria of the NINCDS-ADRDA, they had narrow deficiency, phlegm obstructing intelligence, Qi stagnation, and blood stasis according to syndrome differentiation of TCM.

Patients were excluded if they were ≤55 years old, had a mini-mental state examination (MMSE) score <12, had concomitant diabetes or diabetes history, had concomitant hypertension or hypertension history. The patients who met any one of the above items were excluded.

Patients were removed from the trial if they contracted a serious disease that affected the trial in the observational period, experienced changes in their medication plan, or whose treatment could not be judged due to data loss.

Sixty AD patients consistent with enrollment standards were divided into two groups using a randomized block design. The Bushenhuatanyizhi instant granules (BHY) group included of 30 patients (18 males and 12 females) with an average age of (74±5) years. The piracetam group included of 30 patients (19 males and 11 females) with an average age of (75±6) years. There was no significant difference in educational level among patients (P>0.05). A written informed consent form was obtained from subjects to analyze their diagnostic data retrospectively. The research protocol was approved by the ethics committee of the Hospital of TCM.

Therapeutic methods
Patients in the BHY group took BHY instant granules (6 g, twice per day). BHY was composed of Heshouwu (Radix Polygoni Multiflori), Zhuzieshen (Rhiza Paeoniae), Gucun (Arillus Longan), Shichangpu (Rhizoma Acori Tatarinowii), Zhihu (Caulis Bambusae In Taeniam), Banxia (Rhiza Sassafras), and Fuling (Porzia). The Bushenhuatanyizhi instant granules (6 g, twice per day). BHY was prepared by the Department of Pharmaceutical Preparation of Hubei Hospital of TCM (Wuhan, China) (batch No. 20001006). Piracetam (2-oxo-1-pyrrolidine-acetamide) is a cyclic derivative of gamma-aminobutyric acid. Piracetam has been studied in an extensive number of clinical experiments, and has shown positive results in the treatment of dementia.14,15 Therefore, the control group took piracetam produced by the Northeast General Pharmaceutical Factory (Shen Yang, China) (batch No. 200006066) (0.8 g, 3 times per day). There were twelve weeks in a course. All patients had not taken a drug for the treatment of AD from 2 weeks before the trial to the end of treatment course.
Curative effect assessment
Changes in MMSE or activity of daily living scales (ADL) were observed for AD patients. Comparisons in each group before and after treatment were conducted. The MMSE covers various areas of cognitive domains (e.g., orientation, memory, language, and visual construction) and has become a widely used cognitive screening tool in clinical research due to its brevity and straightforward administration. The ADL is frequently used in clinical trials for AD and assesses patient functional ability.

The MMSE scale is as follows. Very effective: the increase of MMSE score was ≥4 after treatment. Effective: the increase of MMSE score was ≥2, and <4 after treatment. Non-responsive: the increase of MMSE score was <2 after treatment.

The ADL scale is as follows. Very effective: the decrease of ADL score was ≥6 after treatment. Effect: the decrease of ADL score was ≥3, and smaller than 6 after treatment. Invalidation: the increase of ADL score was <3.

Measurement of SOD, LPO and TG in serum
Superoxide dismutase (SOD), lipid peroxide (LPO) and triglyceride (TG) in serum were determined by colorimetric analysis using a spectrophotometer with the associated detection kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). SOD, LPO and LG levels are expressed as U/mL, mol/L and mol/L, respectively.

Statistical analysis
SPSS 10.0 software (SPSS Inc., Chicago, IL, USA) was used to do statistical analysis. T-test was used to do the index comparison, before and after treatment, and the level of significance was \( P < 0.05 \).

RESULTS

MMSE scores before and after treatment
MMSE scores in the two groups increased after treatment and were significantly different after treatment \( (P<0.05) \). However, scores in the two groups were not significantly different after treatment \( (P>0.05) \) (Table 1).

ADL scores before and after treatment
ADL scores in the two groups decreased after treatment and had a significant difference after treatment \( (P<0.05) \). However, scores in the two groups were not significantly different after treatment \( (P>0.05) \) (Table 2).

Clinical effect after treatment
The total effective rate was 86.67% in the BHY group (10 very effective, 13 effective, 7 non-responsive), while the piracetam group was 57.69% (5 very effective, 16 effective, 9 non-responsive) (Table 3).

SOD activities after treatment
The activity of superoxide dismutase (SOD) in the BHY group increased after treatment and had a significant difference from before to after treatment \( (P<0.05) \). However, the content of SOD was not significantly different between the piracetam and BHY groups after treatment \( (P>0.05) \) (Table 4).

LPO content after treatment
The results showed that the content of lipid peroxides (LPO) in the BHY group decreased after treatment and was significantly different after treatment \( (P<0.05) \). However, LPO content was not significantly different between the piracetam and BHY groups after treatment \( (P>0.05) \) (Table 5).

### Table 1. Comparison of MMSE scores before and after treatment (\( \bar{x} \pm s \))

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
<td>15.2±2.5</td>
<td>18.7±2.1'</td>
<td>3.4±1.3</td>
</tr>
<tr>
<td>BHY</td>
<td>30</td>
<td>14.2±1.8</td>
<td>20.7±1.6'</td>
<td>6.1±1.1</td>
</tr>
</tbody>
</table>

Notes: patients in the control group took piracetam; patients in the BHY group took Bushenhuatanyizhi instant granules. MMSE: mini-mental state examination; BHY: Bushenhuatanyizhi. Compared with the same group before treatment, *\( P<0.05 \).

### Table 2. Comparison of ADL in two groups after treatment (\( \bar{x} \pm s \))

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
<td>59.7±6.5</td>
<td>54.3±6.5'</td>
<td>-5.4±1.3</td>
</tr>
<tr>
<td>BHY</td>
<td>30</td>
<td>58.2±7.3</td>
<td>50.4±5.9'</td>
<td>-7.9±1.3</td>
</tr>
</tbody>
</table>

Notes: patients in the control group took piracetam; patients in the BHY group took Bushenhuatanyizhi instant granules. MMSE: mini-mental state examination; BHY: Bushenhuatanyizhi. Compared with the same group before treatment, *\( P<0.05 \).

### Table 3. Comparison of clinical effect in two groups after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Very effective</th>
<th>Effective</th>
<th>Non-responsive</th>
<th>Total effective rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
<td>5</td>
<td>16</td>
<td>9</td>
<td>57.69</td>
</tr>
<tr>
<td>BHY</td>
<td>30</td>
<td>10'</td>
<td>13</td>
<td>7</td>
<td>86.67'</td>
</tr>
</tbody>
</table>

Notes: patients in the control group took piracetam; patients in the BHY group took Bushenhuatanyizhi instant granules. BHY: Bushenhuatanyizhi. Compared with the same group before treatment, *\( P<0.05 \).
**TG content after treatment**

Triglyceride (TG) levels in the BHY group decreased after treatment and differed significantly before and after treatment (P<0.05). However, the TG levels were not significantly different between the piracetam and BHY groups after treatment (P>0.05) (Table 6).

**Safety observation**

Before and after treatment in the two groups, electrocardiogram examination, kidney function, and liver function were normal. This indicated that BHY and piracetam had no obvious toxic effects on the heart, liver, or kidney.

**DISCUSSION**

Neuropsychological testing is very important for AD diagnosis, evaluation, and prognosis. The MMSE and ADL scales are used to measure cognitive function, living activity, and the functions of learning, language, attention, space, and movement. Changes in these testing scores are closely correlated with AD severity.26-28 Our results suggest that Bushenhuatanyizhi instant granules could significantly improve MMSE and ADL scores, increase SOD activity, and decrease the levels of LPO and TG after treatment. So we think, reinforcing kidney-essence, resolving phlegm, and promoting mental therapy can improve cognition and daily activities of AD patients.

In TCM, energy from the kidney is called kidney essence, which can produce marrows including cerebral, spinal cord, and bone marrow. Huang Di Nei Jing said, “The brain is the sea of marrow” and “kidney stores essence to generate marrow”.29 The cerebral marrow can nourish the brain and maintain physiological function. If the kidney essence is insufficient then the production of cerebral marrow will be reduced, leading to various symptoms, such as headache, dizziness, amnesia, and diminished responsiveness.30-33 Meanwhile, TCM holds that all prolonged diseases can be attributed to phlegm. Phlegm-dampness and turbidity obstructing the orifices are the pathogenesis of senile dementia. Once a phlegm obstruction forms, the sea of marrow becomes turbid, the spirit of brain loses nourishment, the original spirit gets blocked, intelligence is damaged, and sudden inspiration and memory become rotten. Therefore, phlegm obstructions can lead to dementia.

We consider, weak kidney-essence and phlegm stasis is the most basic pathogenesis of AD. Prescriptions for AD should follow the principles in Chinese Medicine to reinforce kidney-essence, remove phlegm, and promote mentality.34-36 Therefore, the treatment should take cleaning and nourishing as principles. Clinical treatment should involve “regulating the spirit and improving intelligence” and “supplement deficiency without persisting pathogen”.37,38 Based on these theories, we prescribed BHY which are composed of Heshouwu (Radix Polygoni Multiflori), Zhujiushen (Rhizoma Panax Japonici), Shichangpu (Rhizoma Acori Tatarinowii), Zhuru (Caulis Bambusae In Taeniam), Banxia (Rhizoma Pinelliae), Fuling (Poria), Yuanzhi (Radix Pogge), Gancao (Radix liquiritiae). BHY reinforced kidney-essence, removed phlegm, and promoted mental therapy.39,40 Recent studies showed that Shichangpu (Rhizoma Acori Tatarinowii) tranquilized the mind, enhanced intelligence, and opened orifices. The different fractions of

| Table 4 Comparison of SOD activities in two groups after treatment (U/mL, x ± s) |
|-------------------------------|-------------------|-------------------|----------|
| Group | n | Before treatment | After treatment | Difference |
| Control | 30 | 53.8±5.8 | 58.4±5.5 | -5.4±1.3 |
| BHY | 30 | 54.7±8.5 | 64.3±6.8 | -7.9±1.3 |

Notes: patients in the control group took piracetam; patients in the BHY group took Bushenhuatanyizhi instant granules. SOD: superoxide dismutase; BHY: Bushenhuatanyizhi. Compared with the same group before treatment, *P<0.05.

| Table 5 Comparison of LPO content in two groups after treatment (mol/L, x ± s) |
|-------------------------------|-------------------|-------------------|----------|
| Group | n | Before treatment | After treatment | Difference |
| Control | 30 | 5.34±1.38 | 4.98±0.89 | 0.36±0.49 |
| BHY | 30 | 5.47±1.26 | 4.37±1.02 | 1.10±0.24 |

Notes: patients in the control group took piracetam; patients in the BHY group took Bushenhuatanyizhi instant granules. LPO: lipid peroxides; BHY: Bushenhuatanyizhi. Compared with the same group before treatment, *P<0.05.

| Table 6 Comparison of TG content in two groups after treatment (mol/L, x ± s) |
|-------------------------------|-------------------|-------------------|----------|
| Group | n | Before treatment | After treatment | Difference |
| Control | 30 | 2.34±0.38 | 2.18±0.36 | 0.16±0.02 |
| BHY | 30 | 2.47±0.26 | 1.97±0.42 | 0.50±0.16 |

Notes: patients in the control group took piracetam; patients in the BHY group took Bushenhuatanyizhi instant granules. TG: Triglyceride; BHY: Bushenhuatanyizhi. Compared with the same group before treatment, *P<0.05.
Shichangpu extract such as the soluble and essential oil fractions, could improve the learning and memory abilities in AD mice induced by Aβ42. This effect might be related to the decrease in nitric oxide synthase (NOS) activity. Yuanzhi can significantly improve learning and memory and promote long-term potentiation (LTP) in the hippocampus in vivo. Its mechanism may be related to promoting neurogenesis. In the mouse model of dementia, refined Heshouwu, markedly improved learning memory, lowered the contents of lipofuscin and monoamine oxidase activity in the brain, and enhanced the activities of superoxide dismutase and catalase in the brain and NOS in the hippocampus. Refined Heshouwu could protect the learning and memory capacity of mice with AD, which may be related to the inhibition of apoptosis in the hippocampus. Yuanzhi (Radix Palygalae) dissolved phlegm, opened orifices, and improved learning and memory. Moreover, Yuanzhi (Radix Palygalae) extracts can promote neuronal proliferation in the normal brain and improve memory impaired by scopolamine by inhibiting acetylcholinesterase (AChE) activity. There is suggestive evidence that Fuling (Porzia) could enhance hippocampal LTP and improve scopolamine-induced spatial memory impairment in rats. Fuling (Porzia)’s cognitive action has been ascribed to AChE inhibition and bidirectional regulation of cytosolic free calcium.

In conclusion, reinforcing kidney-essence, resolving phlegm, and promoting mental therapy is effective in alleviating symptoms of dementia, improving cognition dysfunction, and daily function. After a 12-week treatment, cognition and quality of daily life of the patients were improved obviously. There were no obvious changes in experimental detections in the patients or adverse events. Therefore, reinforcing kidney-essence, resolving phlegm, and promoting mental therapy is safe and tolerable.

REFERENCES


