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Clinical observation of the efficacy and mechanism of the Wenfei Jiangzhuo formula in lung and kidney deficiency-type vascular dementia

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ABSTRACT
To explore the clinical efficacy and mechanism of the Wenfei Jiangzhuo formula in lung and kidney deficiency-type vascular dementia. The study was conducted from March 2014 to March 2016. Eighty-four patients with lung and kidney deficiency-type vascular dementia were divided into the observation (n = 44) and control (n = 40) groups. The control group received oral donepezil hydrochloride, while the observation group received the Wenfei Jiangzhuo formula. The mini-mental state examination (MMSE) score, activities of daily living (ADL) scale score, and serum superoxide dismutase (SOD) and malondialdehyde (MDA) levels were assessed before and after treatment. The MMSE and ADL scale scores in the two groups significantly improved after treatment (P < 0.05); the scores in the observation group were significantly higher than those in the control group (P < 0.05). The SOD levels in both groups significantly improved, and there was a significant difference in the MDA levels in both groups (P < 0.05). The SOD and MDA levels improved more significantly in the observation group than in the control group (P < 0.05). The Wenfei Jiangzhuo formula has a good curative effect in patients with lung and kidney deficiency-type vascular dementia and may improve MMSE and ADL scale scores and patient satisfaction.

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KEYWORDS
Clinical efficacy; Wenfei Jiangzhuo formula; lung and kidney deficiency-type vascular dementia; superoxide dismutase; malondialdehyde

Introduction
Vascular dementia (VaD) is a common neurological disease in the elderly with an incidence lower than that of Alzheimer’s disease (AD), which is the second most common cause of dementia (Snyder et al. 2015). VaD is a cognitive dysfunction syndrome arising from brain tissue damage caused by aging, cerebrovascular disease, diabetes, and senile depression. Its clinical manifestations include attention deficits, mental retardation, and word shortage. VaD is caused by the overall or partial effects of vascular disease, which can lead to stroke damage and other issue perfusion changes. It is characterized as a neurocognitive disorder but also includes behavioral symptoms, wall motion abnormalities, and autonomic dysfunction (O'Brien and Thomas 2015; Perneckzky et al. 2016). VaD is closely linked to the spectrum of cerebrovascular disease, and the condition is complex and variable (Venkat et al. 2015). Compared with AD and other types of dementia, VaD has a late onset and is mostly sporadic. However, the average incidence of VaD has been doubling every 5.3 years, which represents a critical problem for clinicians (Qiu et al. 2007).

At present, dementia is recognized as the largest health and social problem worldwide owing to the increasing number of affected patients and the potentially serious threats to the health and safety of individuals. According to statistics from the World Health Organization (Corriveau et al. 2016), the number of patients affected by dementia worldwide has exceeded 47.5 million; with the aging of the population, it is estimated that the number of new cases of dementia may exceed 7.7 million per year. This not only represents significant impacts to patients’ safety and quality of life, but also adds a heavy burden to society and patients’ families. The most common forms of dementia are VaD and AD. VaD is mainly caused by...
the occurrence of ischemia or hemorrhagic disease in the brain, which causes memory and cognitive impairments. Patients may have various other impairments, such as exercise, language, and judgment difficulties (Li et al. 2015). The current pathogenesis of VaD is unclear; however, VaD is a preventable disease that may be reversible by early intervention (Vizcarra et al. 2015).

Lung and kidney deficiency is the name of the disease in traditional Chinese medicine, with this condition resulting in shortness of breath, spontaneous sweating, cold limbs, coughing, abundant expectoration, and other symptoms (Wong and Sagar 2006). The Wenfei Jiangzhuo formula is prepared with six types of herbs, including ginseng, dried ginger, aconite (Radix Aconiti Lateralis Preparata), licorice, rhubarb, and pseudo-ginseng. Radix Aconiti Lateralis Preparata, dried ginger, licorice, and ginseng can strengthen the Yang and inhibit the Yin, whereas rhubarb and pseudo-ginseng can promote blood circulation and other functions. The Wenfei Jiangzhuo formula has been shown to exert an effect on hippocampal neuronal apoptosis in rats with VaD (Hu et al. 2017); however, to our knowledge, there is no relevant report on its clinical treatment efficacy in human subjects.

Therefore, this study explored the clinical efficacy and mechanism of the Wenfei Jiangzhuo formula for the treatment of lung and kidney deficiency-type VaD.

Patients and methods

Clinical data

We retrospectively analyzed 84 patients with lung and kidney deficiency-type VaD who were treated in our hospital from March 2014 to March 2016. The patients were divided into an observation group and a control group according to the treatment administered. A total of 40 patients (22 men and 18 women) with an average age of 65.84 ± 5.84 years (range, 56–79 years) were included in the control group, and 44 patients (25 men and 19 women) with an average age of 66.24 ± 6.14 years (range, 61–82 years) were included in the observation group. The patients in this study met the diagnostic criteria for VaD developed by NINDS-AIREN (Sheen and Sheu 2016) and voluntarily signed consent forms for review by the ethical oversight committee of the First Affiliated Hospital of Guangxi University of Chinese Medicine (No:20131211). Treatment was accompanied by nursing care, with the main purpose to improve patients’ compliance.

Inclusion and exclusion criteria

The inclusion criteria were as follows: age > 55 years, imaging diagnosis of stroke lesions, and no cognitive dysfunction before the stroke. Patients and their families were informed of the study details and consented to undergo treatment. All patients completed the two months of treatment. The exclusion criteria were as follows: patients who had malignant tumors, epilepsy, Parkinson’s disease, schizophrenia, immunodeficiency, and severe mental dysfunction, as well as those who were allergic to this experimental drug.

Treatment method

According to the different therapeutic interventions, the patients were divided into the observation and control groups. The control group was initially treated with 1 tablet/day of donepezil hydrochloride (Zhongguo Weicai Pharmaceutical Co., Ltd., batch number C14200011986; national medicine permission number H20050978, 5 mg/tablet), administered at bedtime; the number of tablets was then increased to 2 tablets/day after 4 weeks. The observation group was treated with one packet (divided into two and administered twice a day, i.e. in the morning and evening with warm water) of the Wenfei Jiangzhuo formula comprising the following: 3 g/package of Radix Aconiti Lateralis Preparata (six packages), 3 g/package of ginseng (five packages), 3 g/package of dried ginger (three packages), 3 g/package of dried ginger (three packages), 3 g/package of rhubarb (three packages), 3 g/package of pseudo-ginseng (three packages), and 3 g/package of licorice (two packages). Both groups were observed for 2 months, and any adverse reactions and changes were recorded. When adverse reactions occurred during the course of treatment, the affected patients were treated promptly; in the event of a serious adverse reaction, treatment was stopped.

Method of detecting the serum superoxide dismutase (SOD) and malondialdehyde (MDA) levels

Serum samples were obtained and centrifuged at 3000 rpm for 10 min. The SOD level was detected using the WST-8 method, and the MDA level was detected using the thiobarbituric acid method (SOD
kit, S0101; MDA kit, S0131, Shanghai Biyuntian Biotechnology Research Institute, Shanghai, China). The SOD detection method was as follows: the sample well and blank wells 1 and 2 were set using a 96-well plate. Thereafter, 160 μL of WST-8 working solution was added to each well and 20 μL of starting solution was added to blank well 1 and the sample well. SOD buffer and 20 μL of serum were added to both blank well 1 and the sample well; 40 μL of serum was added to blank well 2, which was then incubated at 37°C for 30 min. The absorbance value was measured using a microplate reader at 450 mm at 15 min after completion of the incubation. The MDA detection method was as follows: 0.1 mL of homogenate and lysate were added to the centrifuge tube as the blank control group. Thereafter, 0.2 mL of MDA working solution was added to the standard and sample groups, and 0.1 mL of lysate, standard solution, and serum were added to each group. The mixture was then shaken and mixed at 100°C or placed in a boiling water bath for 15 min, cooled in a water bath to reach room temperature, and centrifuged at 1000 g at room temperature for 10 min. Then, 200 μL of the supernatant was added to a 96-well plate, and the absorbance value was measured at 532 nm using a microplate reader (Gao et al. 2019).

**Observation indicators**

Primary observation indicators: The Mini-mental State Examination (MMSE) scores in the two groups were assessed before and after treatment. This scale yields a total score of 30 points, with lower scores indicating more severe cognitive dysfunction. The activities of daily living (ADL) scale scores in the two groups were also evaluated before and after treatment. This scale yields a total score of 100 points, with higher scores indicating better self-care ability. The serum SOD and MDA levels were also assessed before and after treatment.

Secondary observation indicators: The treatment satisfaction and efficacy in the two groups were evaluated. The routine blood test findings and liver and kidney function were assessed before and after treatment. The following formulas were used: Treatment satisfaction = [(total number – general number) / total number * 100%]; total efficacy = [(total number – invalid number) / total number * 100%].

**Statistical method**

The collected data were statistically analyzed using the SPSS software version 20.0 (Shanghai Beka) and

| Table 1. Comparison of baseline characteristics between the two groups of patients [n (%)]. |
|---|---|---|---|---|---|
| Factor | Control group n = 40 | Observation group n = 44 | t/X² value | P value |
| Sex | | | | |
| Male | 22 (55.00) | 25 (56.82) | 0.028 | 0.867 |
| Female | 18 (45.00) | 19 (43.18) | 0.028 | 0.867 |
| Age (years) | | | | |
| ≥ 65 | 29 (72.50) | 30 (68.18) | 0.187 | 0.666 |
| < 65 | 11 (27.50) | 14 (31.82) | 0.187 | 0.666 |
| BMI (kg/m²) | 22.15 ± 1.84 | 22.35 ± 1.66 | 0.524 | 0.602 |
| NHSS score | 7.21 ± 4.80 | 6.84 ± 4.05 | 0.383 | 0.703 |
| Smoking history | | | | |
| Yes | 25 (62.50) | 29 (65.91) | 0.106 | 0.745 |
| No | 15 (37.50) | 15 (34.09) | 0.106 | 0.745 |
| History of hypertension | | | | |
| Yes | 33 (82.50) | 34 (77.27) | 0.355 | 0.552 |
| No | 7 (17.50) | 10 (22.73) | 0.355 | 0.552 |
| Diabetes history | | | | |
| Yes | 32 (80.00) | 32 (73.08) | 0.611 | 0.782 |
| No | 8 (20.00) | 12 (26.92) | 0.611 | 0.782 |
| Hyperlipidemia | | | | |
| Yes | 19 (47.50) | 20 (45.45) | 0.035 | 0.851 |
| No | 21 (52.50) | 24 (54.55) | 0.035 | 0.851 |
| Degree of education | | | | |
| ≥ Junior middle school | 19 (47.50) | 22 (50.00) | 0.052 | 0.819 |
| < Junior middle school | 21 (52.50) | 22 (50.00) | 0.052 | 0.819 |
| Domicile | | | | |
| City | 26 (65.00) | 30 (68.18) | 0.095 | 0.757 |
| Village | 14 (35.00) | 14 (31.82) | 0.095 | 0.757 |
| Patient dementia degree | | | | |
| Mild | 25 (62.50) | 30 (68.18) | 0.229 | 0.584 |
| Moderate | 15 (37.50) | 14 (31.82) | 0.229 | 0.584 |
plotted using GraphPad Prism 7 (Shanghai Beka), in which the count data usage rate (%) was expressed. The chi-square test was also used. The grade data were analyzed using the rank sum test, indicated by Z, and the measurement data were expressed as means ± standard deviations. The measurement data with normal distribution were analyzed using the t-test. Differences between the two groups before and after treatment were analyzed using the paired t-test, expressed as t values. P values < 0.05 were considered to indicate a statistically significant difference.

**Results**

**General information**

We compared the baseline clinical data in the two groups and found no differences (P > 0.05, Table 1).

**Changes in the MMSE and ADL scale scores before and after treatment in the two groups**

We found that the MMSE and ADL scale scores were not significantly different between the two groups before treatment (P > 0.05); however, they became significantly different after treatment. There was a difference in the MMSE and ADL scale scores before and after treatment (P < 0.05), and the scores in the observation group were significantly higher than those in the control group (P < 0.05) (Tables 2 and 3).

**Treatment efficacy in both groups**

In the control group, the treatment was markedly effective in 10 patients, effective in 18 patients, and ineffective in 12 patients; in the observation group, it was markedly effective in 20 patients, effective in 17 patients, and ineffective in 7 patients. The rank sum test revealed a difference in the treatment efficacy between the two groups (Z = -2.102, P = 0.036) (Table 4).

**Changes in the SOD and MDA levels before and after treatment in the two groups**

We compared the SOD and MDA levels before treatment between the two groups and found no difference (P > 0.05). After treatment, the SOD levels in both groups significantly improved, while the MDA levels significantly decreased, with a difference between the two groups (P < 0.05). The improvement in the SOD and MDA levels was significantly greater in the observation group than in the control group (P < 0.05) (Tables 5 and 6).

**Adverse reactions during treatment and treatment satisfaction in both groups**

The routine blood test findings and liver and kidney function in the two groups were significantly different after treatment (P > 0.05). There was no difference in the total incidence of adverse reactions during treatment between the control group and the observation group (X² = 0.291, P = 0.590). The patients’ conditions improved after their respective treatment. In addition, we found that the treatment satisfaction was

| Group | MMSE score variation | ADL score variation |
|-------|----------------------|---------------------|
| Control group (n = 40) | 4.02 ± 1.35 | 6.90 ± 1.84 |
| Observation group (n = 44) | 6.96 ± 2.65* | 11.24 ± 3.84* |

*There was a difference between the values before and after treatment in the control and observation groups (P < 0.05).

**Table 2. Changes in the MMSE and ADL scores after treatment.**

| Group | MMSE score | ADL score |
|-------|------------|-----------|
|       | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment |
| Control group (n = 40) | 16.55 ± 2.68 | 20.84 ± 2.57* | 40.39 ± 6.23 | 47.62 ± 5.31* |
| Observation group (n = 44) | 17.15 ± 2.89 | 23.84 ± 2.43* | 41.22 ± 5.84 | 52.89 ± 5.10* |

*There was a difference between the values before and after treatment (P < 0.05). Indicates P < 0.05 after treatment compared with the control group.

| Group | Excellence | Effective | Ineffective | Total effective rate |
|-------|------------|-----------|-------------|----------------------|
| Control group (n = 40) | 10 (25.00) | 18 (45.00) | 12 (30.00) | 28 (75.00) |
| Observation group (n = 44) | 20 (45.45) | 17 (38.64) | 7 (19.91) | 37 (84.09) |
Table 5. Changes in the MDA and SOD levels after treatment.

| Group                        | Pre-treatment SOD (NU/mL) | Post-treatment SOD (NU/mL) | Pre-treatment MDA (mol/mL) | Post-treatment MDA (mol/mL) |
|------------------------------|---------------------------|----------------------------|---------------------------|----------------------------|
| Control group (n = 40)       | 72.84 ± 16.72             | 85.65 ± 15.39*             | 8.59 ± 2.65               | 6.98 ± 1.37*               |
| Observation group (n = 44)   | 73.15 ± 16.22             | 93.88 ± 14.55*            | 8.87 ± 3.10               | 6.10 ± 1.25*               |
| t value                      | 0.086                     | 2.531                     | 0.443                     | 3.079                      |
| P value                      | 0.931                     | 0.013                     | 0.659                     | 0.003                      |

*There was a difference between the values before and after treatment (P < 0.05). #Indicates P < 0.05 after treatment compared with the control group.

Table 6. Comparison of the differences in MDA between the two groups.

| Group                        | SOD (NU/mL) variation | MDA (mol/mL) variation |
|------------------------------|-----------------------|------------------------|
| Control group (n = 40)       | 11.18 ± 4.25          | 2.02 ± 0.63            |
| Observation group (n = 44)   | 19.18 ± 5.84*         | 3.02 ± 1.12*           |
| t value                      | 7.117                 | 4.975                  |
| P value                      | 0.000                 | 0.000                  |

*There was a difference between the values before and after treatment in the control and observation groups (P < 0.05).

Table 7. Treatment satisfaction in both groups [(n %)].

| Group                        | Very satisfied | Satisfied | Neutral |
|------------------------------|----------------|-----------|---------|
| Control group (n = 40)       | 12 (30.00)     | 15 (37.5) | 13 (32.5)|
| Observation group (n = 44)   | 15 (34.09)     | 23 (52.27)| 6 (13.64)|

significantly greater in the observation group than in the control group (X^2 = 4.079, P = 0.044) (Table 7).

Discussion

Traditional Chinese medicine believes that the main function of the lung is governing Qi to control respiration, as well as governing water, which connects the vessels and plays a role in dispersing and descending energy (May et al. 2016). The kidney houses the essence. If the patient has innate kidney essence deficiency, the postnatal essence cannot nourish the spleen and stomach, which leads to disorders of the qi and blood, failure of the spleen qi to ascend, and qi and blood not filling the brain. According to the five element cycles that belie our physiological balance, kidney is connected to water, lung is connected to metal, and metal generates water, making the lung the mother of the kidney.

Some studies have shown that the incidence of VaD is closely related to lung deficiency and dysfunction (Maciocia 2015). If deficiency of lung and kidney-yang leads to lung deficiency, the brain orifice cannot be properly warmed and nourished, resulting in a deficiency in the energy and substance of the brain. The body will show turbid toxins, phlegm and dampness, blood stasis, and other pathological accumulations, all of which contribute to the development of dementia or other performance impairments. The Wenfei Jiangzhuo formula is primarily composed of ginseng, dried ginger, **Radix Aconiti Lateralis Preparata**, honey-fried licorice, rhubarb, and **Panax Notoginseng**. According to traditional Chinese medicine, the main pathological mechanism of VaD involves deficiency of the patients’ source energy and yang causing heart, liver, spleen, lung, and kidney weakness, thereby leading to mental disorders, which may be improved by the consumption of aconite and dried ginger (Qiang et al. 2015). **Radix Glycyrrhizae** and **Radix Ginseng** are used to nourish yang, smooth qi, and activate blood circulation to remove turbidity. In this study, use of the Wenfei Jiangzhuo formula to treat patients with lung and kidney deficiency-type VaD showed good clinical efficacy and may be considered a viable clinical treatment option.

Donepezil hydrochloride is the main therapeutic drug for VaD and AD, and it has a good treatment effect in patients with mild-to-moderate dementia (Liu et al. 2016). Traditional Chinese medicine combined with Western medicine has shown good treatment effect in patients with VaD as well, with positive effects on patient recovery (Wang et al. 2015). In this study, we evaluated the treatment efficacy rate in the two groups and found that the total treatment efficacy rate in the control group was significantly lower than that in the observation group. This indicates that the combination of donepezil hydrochloride and the Wenfei Jiangzhuo formula may effectively improve patients’ conditions to a certain degree. In addition, we evaluated the patients’ MMSE and ADL scale scores. The MMSE score is the main scoring standard for patients with dementia that can comprehensively, accurately, and quickly reflect patients’ self-care abilities and cognitive function (Cagnin et al. 2015). The ADL scale score is used to evaluate the patients’ ability to perform ADL. A previous study has shown that treatment efficacy can be accurately assessed by observing changes in the patients’ MMSE and ADL scale.
scores (Toots et al. 2016), which we analyzed before and after treatment in both groups in the present study. We found that the MMSE and ADL scale scores improved after treatment in both groups; however, the scores were significantly higher in the observation group than in the control group. This finding illustrates the greater improvement in the cognitive function and quality of life of the patients in the observation group who were treated with the Wenfei Jiangzhuo formula and donepezil hydrochloride. However, the mechanism of action of the Wenfei Jiangzhuo formula and whether it regulates related factors remain unclear.

With the recent investigation of the pathogenesis of VaD and AD, the scope of research has expanded. Oxygen free radical formation and oxidative stress are the main pathogeneses of VaD (Kim et al. 2015). When a patient develops brain damage or reperfusion, a chain reaction occurs owing to significant free radical release, which increases cell membrane permeability, and a large amount of toxic edema, and excitatory transmitters are released. At the same time, the intracellular calcium ion concentration increases, which aggravates brain cell damage and eventually causes delayed neuronal necrosis. MDA is a lipid peroxidation end product, and its expression can directly reflect the level of free radical production and the degree of lipid peroxidation, which is often used as an index to evaluate the degree of free radical damage to the body (Liu et al. 2018). As an important antioxidant enzyme in the body, SOD is an oxygen radical scavenger that maintains the dynamic balance of oxygen free radicals in the body (Ragy and Kamal 2017). Clinical studies have shown that the MDA and SOD expression levels in patients with AD may reflect their intelligence status (Xu et al. 2014), which may indicate that MDA and SOD can be used as markers of cognitive function and memory decline in patients with dementia. Therefore, in this study, we examined the serum expression of MDA and SOD and found that levels improved after treatment. However, the improvement in the observation group was significantly better than that in the control group, which suggests that the Wenfei Jiangzhuo formula may directly impact MDA and SOD expression. However, the exact way in which it affects patients’ conditions needs to be clarified in animal studies.

Along with the MDA and SOD levels, the findings of routine blood, urine, and stool tests, electrocardiogram studies, and liver and kidney function were assessed in the two groups. No differences were observed between the groups, and the incidence of adverse reactions was also not significantly different, which demonstrates that the two regimens are not associated with obvious adverse reactions and yield good effects. Finally, the patients’ satisfaction after treatment was evaluated. We found that the treatment satisfaction was significantly greater in the observation group than in the control group, which indicated that the treatment of the patients with lung and kidney deficiency-type VaD with the Wenfei Jiangzhuo formula did not increase the incidence of the adverse reactions. Furthermore, the treatment also enhanced patient satisfaction, thereby optimizing the doctor-patient relationships. However, there are some limitations in this study. First, the patients were not followed up for a long time period, and the long-term impact of the treatments remains unclear. Second, the sample sizes were small owing to a limited number of eligible patients. In addition, there are differences in the physical conditions of patients across different geographic regions. Therefore, it is necessary to validate the efficacy of the Wenfei Jiangzhuo formula in European and American populations. Finally, it remains unknown how the Wenfei Jiangzhuo formula affects patients with VaD considering that it appears to regulate the in vivo expression of MDA and SOD. Therefore, we hope to conduct follow-up treatments in the future, with an increased number of samples and patients from different regions, and to perform in vitro or animal experiments to elucidate the mechanism behind the effects of the Wenfei Jiangzhuo formula on MDA and SOD expression.

In summary, the Wenfei Jiangzhuo formula demonstrated a good treatment effect in patients with lung and kidney deficiency-type VaD, with improved MMSE and ADL scale scores and patient satisfaction. Its effects may be attributable to the regulation of SOD and MDA levels.

Disclosure statement
No potential conflict of interest was reported by the author(s).

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