Clinical effect of Shibing Xingnao granules on vascular dementia patients and its effect on serum neuronal apoptosis molecules

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ARTICLE INFO	ABSTRACT
Original paper *Article history:* *Received: November 23, 2022* *Accepted: February 16, 2023* *Published: February 28, 2023* *Keywords:* *TALNEC2, miR-19a-3p, JNK, cerebral infarction, cell viability, inflammation, apoptosis*	It was intended to study the clinical effect of Shibing Xingnao Granules on patients with vascular dementia (VD) and to explore its effect on serum neuronal apoptosis molecule levels in VD patients. For this purpose, 78 VD patients, as research objects, were grouped into a control group (acupuncture therapy) and an observation group (acupuncture therapy + Shibing Xingnao Granules) using the random number table method, with 39 cases per group. The clinical effect, cognitive function, neurological function, activity of daily living (ADL) score, and serum B-cell lymphoma-2 (Bcl-2), Bcl-2 associated X protein (Bax), as well as Caspase-3 (Casp3) levels in two groups were observed. Results showed that the markedly effective rate (MER) (82.05%) and total effective rate (TER) (100%) in the observation group were higher than the control group (56.41%, 92.31%) ($P<0.05$). After treatment, the Mini-mental State Examination (MMSE) score, the distributions of mild VD and normal patients, ADL score, and Bcl-2 level were higher in the observation group than in the control group. National Institutes of Health Stroke Scale (NIHSS) score, Bax, and Casp3 levels were lower in the observation group ($P<0.05$). The conclusion was that Shibing Xingnao Granules could further enhance the therapeutic effect of VD patients, and could increase Bcl-2 level and reduce Bax and Casp3 levels.

Introduction

Dementia is a mental disease obstructing people over 60 years old in China. The most common types of this disease are vascular dementia (VD) and Alzheimer's disease (1,2). The incidence of VD in China is on an increasing trend in recent years, second only to Alzheimer's disease. The proportion is about 1.5% of the elderly over 65 years old suffer from VD in China. At present, patients with VD account for 10-20% of the total number of dementia cases (3,4). VD is caused by brain damage due to cerebral vascular lesions or related risk factors (5). The main clinical manifestations are serious injury to memory function, attention function, cognitive function, language expression function, and executive function (6). VD is sudden and progressive with steps and fluctuation (7). VD easily leads to the impairment of patients' self-care ability in daily life. This not only increases the energy of families to take care of patients but also causes a greater economic and spiritual burdens to families and society. Studies have also found that VD can be reversible if reasonable and effective intervention is given at an early stage (8).

With the deepening of people's understanding of tra-

ditional Chinese Medicine (TCM) in recent years, TCM therapy has been explored and applied by more and more experts in treating VD. At current, experts have applied acupuncture, moxibustion, and other TCM therapies to VD treatment and achieved good outcomes (9,10). At the moment, however, the major treatment for VD is medication. TCM believes that the pathogenesis of VD patients is brain emptiness or pathogenic factors going up for disturbance of lucid orifices. It leads to dysplasia or confusion of the lucid orifices, which is mostly the syndrome of asthenia in origin and health in superficiality, intermingled deficiency and excess. According to the pathogenesis of VD in TCM, some physicians designed a prescription named Shibing Xingnao prescription and combined it with acupuncture for the treatment of VD. It was also illustrated that Shibing Xingnao prescription combined with acupuncture had a better clinical effect (11). Upon inquiry, Shibing Xingnao Granules have been applied for production and supply. However, at present, the clinical application of Shibing Xingnao Granules is very lacking, and further research support is still needed. Modern medicine believes that neuronal cell apoptosis is a crucial pathogenesis of VD and other nervous system diseases (12).

Factors associated with neuronal apoptosis include B-cell lymphoma-2 (Bcl-2), Bcl-2 associated X protein (Bax), Caspase-3 (Casp3), and others. Bcl-2, Bax, and Casp3 can inhibit or promote the apoptosis of neurons; therefore, the regulation of neuronal apoptosis-related factors has a certain effect on VD control. Some studies have also proved that TCM therapy can play a role in the anti-apoptosis of nerve cells by regulating levels of Bcl-2, Bax, and other factors related to nerve apoptosis (13). Nevertheless, there is no clinical study about the influence of Shibing Xingnao Granules on factors related to nerve apoptosis.

Thus, this work would study not only the clinical effect of Shibing Xingnao Granules on patients with VD, but also its influence on the serum neuronal apoptosis molecules Bcl-2, Bax, and Casp3 levels in patients. It was to offer further research support and a relevant treatment basis for Shibing Xingnao Granules in the clinical treatment of VD.

Materials and Methods

Research objects

78 VD patients admitted to the Second Affiliated Hospital of Anhui University of Chinese Medicine from January 2020 to June 2022 were enrolled as objects. Inclusion criteria were: all VD patients met *Criteria for Diagnosis, Syndrome Differentiation, and Efficacy of Vascular Dementia* (14); All the patients were 50-80 years old; had a history of stroke; Hanchinski Ischemia Scale (15) was taken for all patients before treatment, and the score was >7; All patients/family members had been informed of this project and had signed informed consent. Exclusion criteria were composed of: Patients accompanied by other mental disorders; Had diseases of the hematopoietic system; Accompanied by severe heart, liver, and kidney dysfunction; Functional impairment due to non-vascular diseases; Had a history of drug, alcohol, and substance abuse, affected the researchers' assessments of cognitive function. In this work, there were 47 male cases and 31 female cases, with the course of the disease 3-18 months. This project had been approved by the relevant medical ethics committee.

Grouping

78 patients with VD were grouped into a control group and an observation group in the random number table method, with 39 cases in both. the control group received conventional acupuncture therapy for symptomatic treatment. There were 25 male cases and 14 female cases in this group. The patients ranged in age from 54-80 years old, having an average age of (60.78 ± 7.32) years old. The course of the disease ranged from 4-18 months, with an average course of (12.63 ± 3.77) months. In accordance with the clinical dementia rating (CDR) scale (16), 6, 24, and 9 patients were assessed with mild, moderate, and severe dementia, respectively. In addition to conventional acupuncture therapy, the observation group combined with Shibing Xingnao Granules treatment; there were 22 male patients as well as 17 female patients. These patients were 50-79 years old, having an average age of (57.45 ± 7.01) years old; the course of disease ranged from 3-18 months, with an average course of (13.88 ± 3.23) months. There were also 5 cases with mild dementia, 27 cases with moderate dementia, and 7 cases with severe dementia in the observation group. None of the significant statis-

tical differences were discovered in gender, age, course of the disease, and severity of dementia between groups (P>0.05), suggesting that the study was feasible.

Therapeutic methods

The control group adopted conventional acupuncture treatment. Main acupoints were Baihui, Yintang, Fengfu, Shenting, Fengchi, Renzhong, Dazhui, Taixi, etc. The acupuncture method was as follows. The patient was instructed to take a seated position and the skin was sterilized before acupuncture. 1/1.5 disposable stainless steel acupuncture needles (Hwato Brand, Suzhou Medical Appliance Factory) were taken for acupuncture. The needles were retained for 30 minutes each time, 6 times a week, for 4 courses of treatment (4 weeks as a course of treatment).

The observation group took Shibing Xingnao Granules in addition to conventional acupuncture treatment. The prescription of Shibing Xingnao Granules was composed of 8 g grass-leaf sweet flag rhizome (dried product), 10 g milkwort root, 10 g Sichuan lovage rhizome, and 0.05 g borneol. It had a specification of 0.5 g/granule, and it should be administrated orally, 5 granules/time, 3 times/day, as the same for 4 courses of treatment.

Detection indicators

About 3 mL of peripheral venous blood was extracted from patients during and after treatment on an empty stomach. The blood sample was centrifuged for 10 min at 3,000 r/min using a high-speed bench centrifuge (Cence Centrifuge Instrument Co., Ltd., Model: L600). The supernatant was taken, and the contents of Bcl-2, Bax, and Casp3 in the serum of patients were detected by double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) (R&D Systems, the United States).

Observation indicators

Assessment of cognitive function

Mini-Mental State Examination (MMSE) (17) was adopted to assess patients' cognitive function. There were 30 questions in 7 dimensions including time/place orientation, immediate/delayed memory, attention and calculation, language, and visual space. The full score was 30; when a patient's MMSE score was lower than 27, it indicated that the patient had cognitive dysfunction. The lower the MMSE score was, the more serious the cognitive dysfunction was. Conversely, a score of 27 or above meant normal cognitive function.

Neurological function assessment

In this work, the National Institute of Health Stroke Scale (NIHSS) (18) was taken to the evaluation of the neurological function of the patients. It covered 11 dimensions such as consciousness, gazing, visual field, and sensation, with a total score of 45. The lower the NIHSS score, the better the recovery of neurological function.

Assessment of dementia severity

CDR was adopted to assess the severity of VD before and after treatment. The scale mainly included several dimensions, such as memory, orientation, problem-judging and problem-solving ability, social activities, housework and hobbies, and personal life ability. The mean of the sum of scores of each dimension was taken. The specific rating

standard was: 0 for healthy, 0.5 for suspected, 1 for mild, 2 for moderate, and 3 for severe.

Assessment of daily living

The activity of Daily Living (ADL) Scale (19) was adopted to assess the patients' daily living ability, which mainly included two parts: the physical life self-maintenance scale and the instrumental ADL scale. This study focused on the former, with 10 questions in total and a total score of 100. When the ADL score was less than 20, it suggested that the patient had a serious functional defect; the higher the ADL score was, the better the patient's ADL capability was.

Effect evaluation

The therapeutic effects of the two groups were compared, and the specific evaluation criteria were as follows. For a marked effect, the main symptoms, ability to answer questions, self-maintenance ability, and orientation were basically normal, and the syndrome score was reduced by more than 75% compared with before treatment. Effective was, the main clinical symptoms were relieved, the questions were answered correctly, some help from family members was needed in life, there were minor mental and personality disorders, and the syndrome score was reduced by 35%-75% compared with before treatment. Ineffective was, no significant improvement or even aggravation of main clinical symptoms was observed, and the syndrome score decreased not more than 35% compared with before treatment. The evaluation criteria of symptom score were: 0, asymptomatic; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms. The calculation method of symptom score reduction rate was shown as Equation 1. The markedly effective rate (MER) and total effective rate (TER) were counted as Equation 2 and Equation 3, respectively.

$$Rate_{Effctive} = \frac{N_{Effctive}}{N_{all}} \times 100\%$$
[1]

$$Rate_{Effctive} = \frac{N_{Effctive}}{N_{all}} \times 100\%$$
[2]

$$Rate_{TE} = \frac{N_{Effctive} + N_{Valid}}{N_{all}} \times 100\%$$
[3]

In the above equations, $Rate_{Score}$ represented the reduction rate of syndrome score, $Score_{before}$ was the score before treatment, and $Score_{after}$ was the score before treatment. $Rate_{Effctive}$ represented MER of treatment, $Rate_{TE}$ represented TER of treatment. $N_{Effctive}$ was the number of markedly effective cases, and N_{Valid} was the number of effective cases.

Methods for statistics

SPSS 22.0 was applied to analyze and process research data. t-test was used for comparisons of measurement data between groups, as the data were described in (x ± s). Enumeration data were expressed as a percentage (%) under ^{2} test. $P<0.05$ indicated that the differences were statistically significant.

Results

Comparison of cognitive function before and after treatment

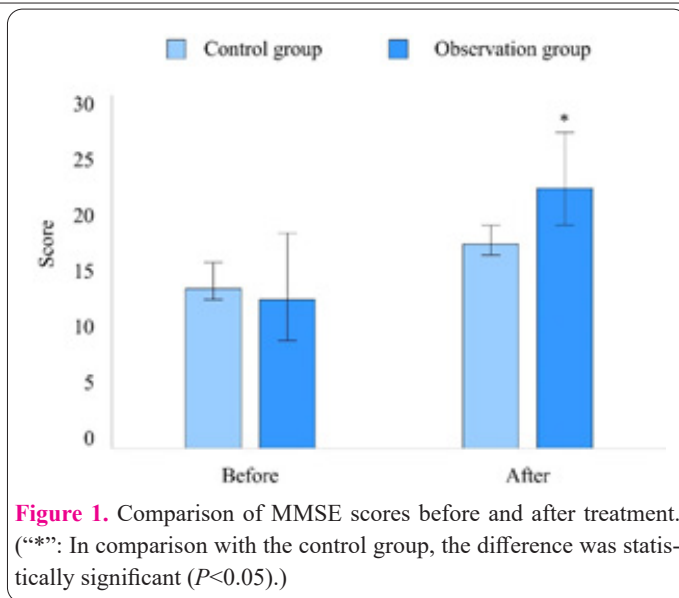Figure 1 showed the comparison of MMSE scores be-

Figure 1. Comparison of MMSE scores before and after treatment. ("*": In comparison with the control group, the difference was statistically significant ($P<0.05$).)

fore and after treatment between groups. Before treatment, the MMSE score of the control group was (13.67 ± 2.89), while that of the observation group was (12.98 ± 2.53), without any significant statistical difference ($P>0.05$). After treatment, the MMSE score reached (15.82 ± 2.75) in the control group and (21.76 ± 3.32) in the observation group. MMSE score was higher in the observation group than the control group after treatment, and there was a significant statistical difference ($P<0.05$).

Comparison of neurological function before and after treatment

Figure 2 compared NIHSS scores between groups before and after treatment. Before treatment, the NIHSS score was worked out as (28.82 ± 5.12) of the control group and (29.33 ± 5.61) of the observation group, without any significant statistical difference ($P>0.05$). After treatment, the NIHSS score changed to (26.68 ± 4.08) for the control group and (17.85 ± 3.45) for the observation group. The NIHSS score was lower in the observation group than in the control group after treatment, with a significant statistical difference ($P<0.05$).

Comparison of dementia severity before and after treatment

Table 1 displayed the assessment results of the severity of dementia in two groups before and after treatment.
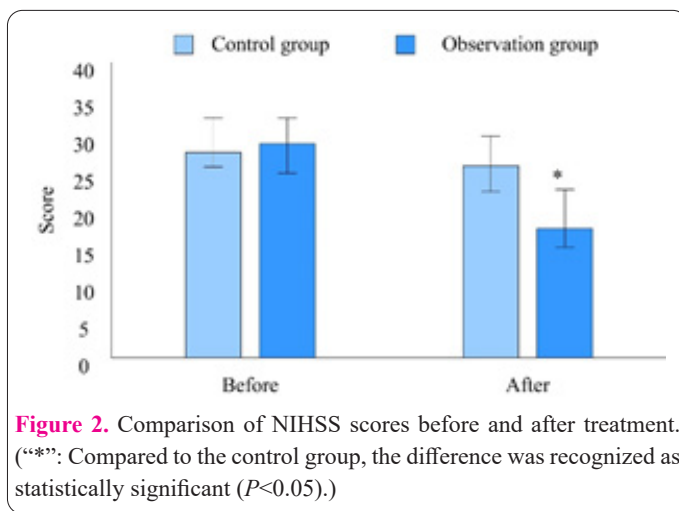

Figure 2. Comparison of NIHSS scores before and after treatment. ("*": Compared to the control group, the difference was recognized as statistically significant ($P<0.05$).)

Table 1. Statistics of the assessment results of dementia severity before and after treatment.

Severity of dementia	Before treatment		After treatment	
	Control group (n=39)	Observation group (n=39)	Control group (n=39)	Observation group (n=39)
Basically normal	0	2	0	7
Mild	6	20	5	26
Moderate	24	12	27	4
Severe	9	5	7	2

In the control group before treatment, there were 6 cases of mild dementia, 24 cases of moderate dementia, and 9 cases of severe dementia. In the observation group, 5, 27, and 7 cases had mild, moderate, and severe dementia, respectively. After treatment, 2 cases were normal, 20 cases had mild dementia, 12 cases had moderate dementia, and 5 cases had severe dementia in the control group. In the observation group, dementia was rated as basically normal, mild, moderate, and severe in 7, 26, 4, and 2 cases, respectively.

According to Table 1, before treatment, 15.38% of patients in the control group and 12.82% in the observation group were mild or basically normal. There was not any significant statistical difference in the distribution of mild dementia and normal patients between groups ($P>0.05$). After treatment, 56.41% of patients were mild and normal in the control group, while 84.62% were in the observation group. The distribution of patients with mild dementia and basically normal patients was higher in the observation group than the control group, with a significant statistical difference ($P<0.05$) as displayed in Figure 3.

Comparison of ADL between groups before and after treatment

Figure 4 showed the comparison of ADL scores between groups before and after treatment. Before treatment, the ADL score was counted as (36.24 ± 3.94) for the control group and (37.92 ± 3.88) for the observation group, without any significant statistical difference ($P>0.05$). After treatment, the ADL score became (47.37 ± 4.67) of the control group and (54.49 ± 4.83) of the observation group. The ADL score was higher in the observation group than in the control group with a significant statistical difference ($P<0.05$).

Comparison of therapeutic effects between groups

According to statistics, in the control group, there were 22 patients with markedly effective treatment, 14 patients with effective treatment, and 3 patients with ineffective treatment. In the observation group, there were 32, 7, and 0 patients with markedly effective, effective, and ineffective treatment, respectively. By calculation, the MER of the control group was 56.41%, and TER was 92.31%. In the observation group, MER reached 82.05% and TER
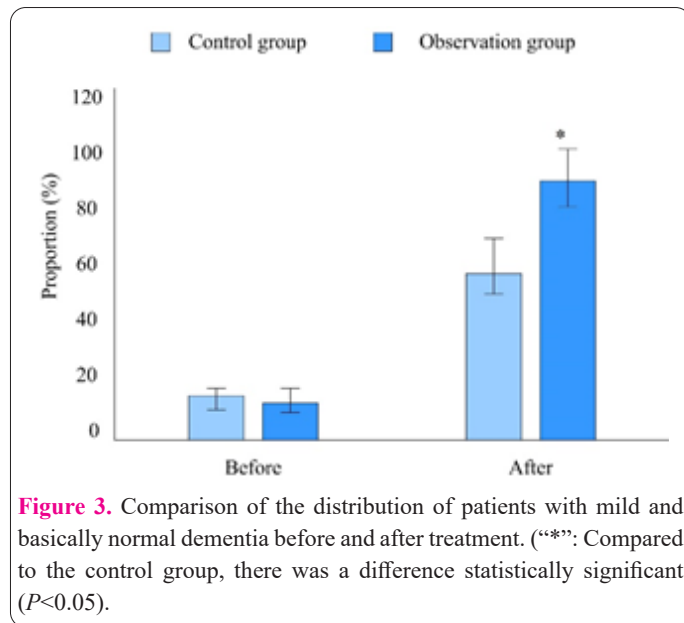

Figure 3. Comparison of the distribution of patients with mild and basically normal dementia before and after treatment. ("*": Compared to the control group, there was a difference statistically significant ($P<0.05$).
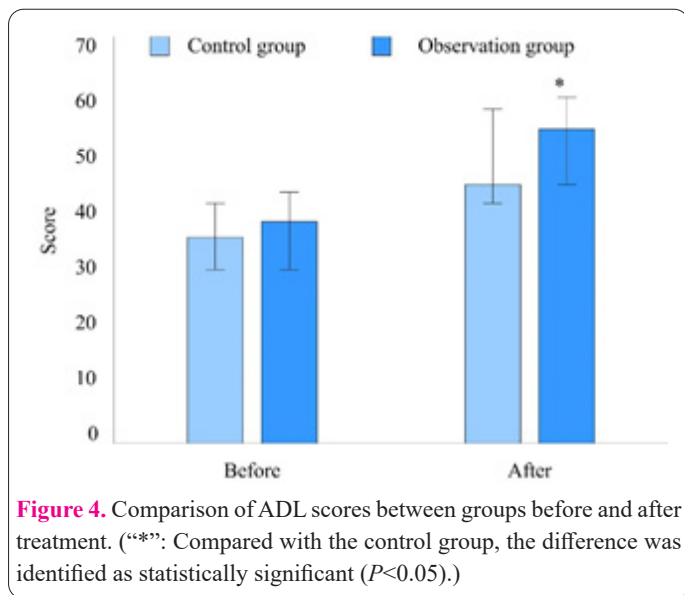

Figure 4. Comparison of ADL scores between groups before and after treatment. ("*": Compared with the control group, the difference was identified as statistically significant ($P<0.05$).)

reached 100%. The MER and TER were higher in the observation group than the control group, showing significant statistical differences ($P<0.05$) as could be observed in Table 2.

Table 2. Statistical comparison of therapeutic effects between the groups.

Therapeutic effect	Markedly effective	Effective	Ineffective	MER	TER
Control group (n=39 cases)	22	14	3	56.41%	92.31%
Observation group (n=39 cases)	32	7	0	82.05%	100%
P	0.021*	0.009*	0.012*	0.003*	0.013*

("*" indicated the differences having statistical significance ($P<0.05$).)

Comparison of serum neuronal apoptosis molecules before and after treatment

ELISA method was adopted to detect serum neuronal apoptosis molecules Bcl-2, Bax, and Casp3 in two groups before and after treatment. The results were compared and presented in Figure 5. There was not any significant statistical difference in Bcl-2, Bax, and Casp3 levels between groups before treatment (*P*>0.05). After treatment, the Bcl-2 level was higher in the observation group than in the control group, while Bax and Casp3 levels were lower than the control group, showing significant statistical differences (*P*<0.05).

Discussion

VD belongs to the category of dementia and dullness disease in the internal medicine of TCM. There is relatively little research about dementia in ancient medical collections. After continuous exploration and improvement by doctors, TCM believes that dementia is mainly caused by aging, congenital deficiency, acquired spleen and stomach dystrophy, emotional changes, and long stagnation of pathogenic factors. These are mostly intermingled with deficiency and excess; therefore, the treatment principle is mainly to supplement deficiency and reduce excess. At present, clinical studies of the use of TCM therapy have been quite common, and most of them have achieved good results (20,21). However, most of the researches are about acupuncture and relatively few studies are about the application of TCM herbs. In this work, Shibing Xingnao Granules assisted acupuncture therapy was used for the treatment of VD. As a result, the MER (82.05%) and TER (100%) of cases in the observation group were higher than those (56.41%, 92.31%) in the control group (*P*<0.05). It was suggested that the therapeutic effect of patients with the assistance of Shibing Xingnao Granules was more significant. Borneol in Shibing Xingnao Granules has the function of inducing resuscitation and is often used to blockage syndrome, dizziness, convulsion, and so on. In addition, modern medical research has also found that borneol has the effect of opening the blood-brain barrier, which can promote various medicines to play their roles in the brain (22). Grass-leaf sweet flag rhizome and milkwort root in the prescription have the functions of expelling phlegm, inducing resuscitation, calming the mind, and reinforcing intelligence. The combination of the two has a better therapeutic effect. Sichuan lovage rhizome leads the medicine upward, to enable the medicine to reach the disease position and further play its role (23,24). Therefore, Shibing Xingnao Granules are effective in the treatment of VD. After treatment, the MMSE score, distribution of mild dementia and basically normal patients, and ADL score of the observation group were higher than the control group, while the NIHSS score was lower (*P*<0.05). The results illustrated that Shibing Xingnao Granules could better improve the cognitive function, neurological function, and dementia severity of patients, and could effectively improve ADL of patients. This also demonstrated that TCM symptomatic treatment has good application value in VD. Chan et al. (2018) (25) also analyzed the application of Chinese herbs in VD and found 7 Chinese herbs with huge potential benefits in the treatment of VD.

Another study (2022) (26) has also proposed that the active ingredients in Chinese herbal medicines can im-
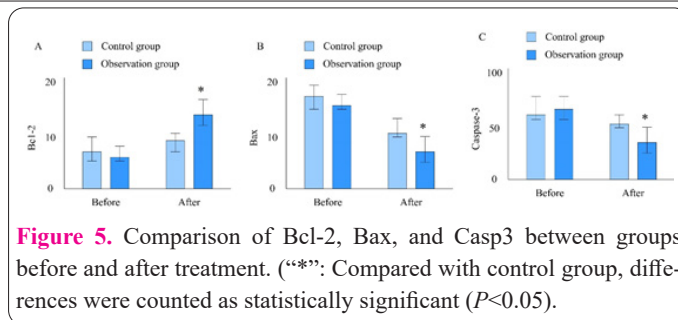

Figure 5. Comparison of Bcl-2, Bax, and Casp3 between groups before and after treatment. ("*": Compared with control group, differences were counted as statistically significant (*P*<0.05).

prove the cognitive function of patients by regulating the apoptosis of hippocampal cell apoptosis. This work also showed that after treatment, the Bcl-2 level was higher in the observation group than the control group, and Bax and Casp3 levels were lower (*P*<0.05). It was suggested that the Chinese herbal medicines in Shibing Xingnao Granules could regulate the serum neuronal apoptosis molecules of patients, so as to improve the clinical symptoms of VD patients. Moreover, many studies have confirmed that TCM can effectively treat VD diseases by inhibiting autophagy and apoptosis of hippocampal neurons (27,28). However, at present, no relevant studies have directly confirmed the molecular regulation effect of TCM in Shibing Xingnao Granules on serum neuronal apoptosis. Therefore, the results of this work need further confirmation.

In summary, the clinical effect of Shibing Xingnao Granules on VD patients was explored and its influence on serum neuronal apoptosis molecules was analyzed. Therefore, this study concluded that the adjuvant therapy of Shibing Xingnao Granules could further enhance the therapeutic effect of VD patients, improve Bcl-2 levels, and reduce Bax and Casp3 levels. However, there was a lack of studies about the molecular regulation effect of medicines in Shibing Xingnao Granules on serum neuronal apoptosis, so further research was still required. Nevertheless, the study proved that TCM therapy had a great prospect in clinical diseases in the future.

Funding

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