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# ***Yizhi Xingnao* prescription improves the cognitive function of patients after a transient ischemic attack\***

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## **Abstract**

Patients with mild cognitive impairment after a transient ischemic attack were included in this study. They were treated with *Yizhi Xingnao* prescription, ergoloid mesylates or aspirin for 60 days. Evaluation using the Montreal Cognitive Assessment Scale showed that cognitive function was significantly improved in all patients, especially after the combined treatment of *Yizhi Xingnao* and aspirin. The scores from the Montreal Cognitive Assessment Scale were improved overall and the effective treatment rate was as high as 79%, which was higher than patients treated with a combination of ergoloid mesylates and aspirin, or aspirin alone. Our experimental findings indicate that *Yizhi Xingnao* prescription can improve mild cognitive impairment after a transient ischemic attack, and that it is more effective than ergoloid mesylates.

**Key Words:** *Yizhi Xingnao* prescription; transient ischemic attack; mild cognitive impairment; Montreal Cognitive Assessment Scale; ergoloid mesylates; aspirin

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## **INTRODUCTION**

Transient ischemic attack (TIA)-caused cerebral ischemic impairment may lead to pathological damage in cognitive-related regions such as the hippocampal CA1 region, thalamus and temporal cortex, thus triggering cognitive dysfunction<sup>[1-3]</sup>. A number of existing studies has shown that an early TIA is characteristics of mild cognitive impairment (MCI)<sup>[4-5]</sup>, which is scarcely detected clinically at the early stage and gradually aggravates until dementia occurs as a result of a decline in intelligence. A TIA is an important risk factor for vascular dementia and Alzheimer's dementia, and it can exacerbate the degeneration of the brain and the decline of cognitive function<sup>[6]</sup>. Therefore, intervention in cognitive impairment is important after a TIA. Numerous studies suggest that spatial cognitive impairment at an early stage of cerebral ischemia may be associated with a defect in the hippocampal cholinergic pathway and neuropeptide dysfunction<sup>[7-9]</sup>. Thus, improving blood flow to the ischemic area, reducing the frequency of TIA recurrence, and restoring neuronal signal transduction pathways may be effective ways of improving cognitive impairment following a TIA.

Clinical studies have found *Yizhi Xingnao*

prescription has an apparent effect on the treatment of vascular dementia, but the Mini-Mental State Examination and other scales displayed a limited effect of this prescription for the improvement of cognitive function<sup>[10]</sup>. Meta analysis regarding the treatment for vascular dementia confirmed that the traditional Chinese medicine cannot improve the Mini-Mental State Examination score in vascular dementia patients<sup>[11]</sup>.

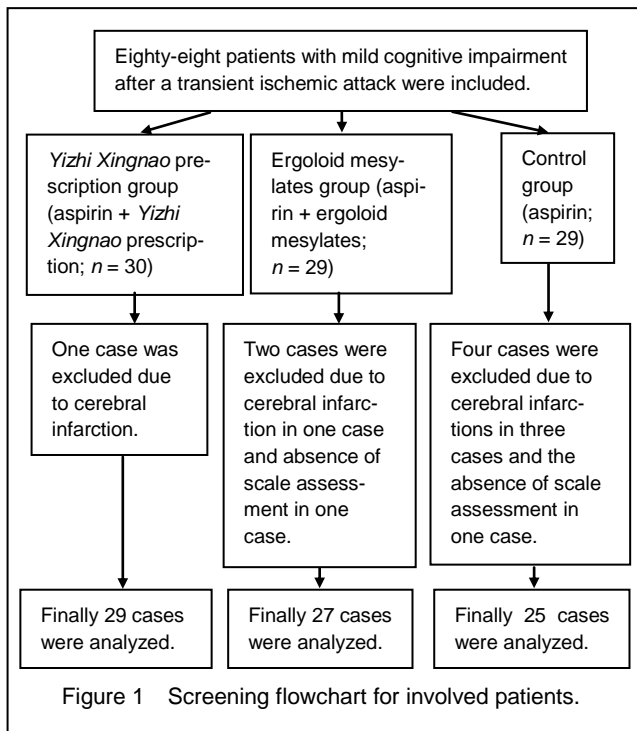
In this study, patients associated with MCI after a TIA were treated with *Yizhi Xingnao* prescription and their cognitive function was determined using the Montreal Cognitive Assessment (MoCA) scale. While ergoloid mesylates, a western drug used for the clinical treatment of vascular cognitive impairment, and aspirin, both of which have been shown to inhibit platelet aggregation and prevent a TIA<sup>[12]</sup>, served as controls.

## **RESULTS**

### **Quantitative analysis of subjects**

In total, 88 patients with MCI after a TIA were recruited from the Third Affiliated Hospital of Nantong University, China from 2007 to 2010. Patients were divided into three groups according to the random digital number table (orders of admission numbers). After 60 days of the corresponding treatments, the results from 81 patients

were included in the study (seven patients were excluded due to cerebral infarction or absence of scale assessment). The screening and grouping management is shown in Figure 1.



**Baseline information of subjects**

Baseline information of the 88 patients is shown in Table 1. There was no significant difference among the three groups in terms of age, gender, educational level, TIA frequency and cognitive function ( $P > 0.05$ ). The total score and sub-scale score of MoCA showed no statistically significant difference among the three groups before treatment ( $P > 0.05$ ; Table 2).

Table 1 Comparison of baseline information in the three groups

Item	Yizhi Xingnao prescription group (n = 30)	Ergoloid mesylates group (n = 29)	Control group (n = 29)	P
Gender (male/female, n)	17/13	14/15	12/17	0.500
Age (year)	64.3±8.0	62.3±9.6	61.6±10.8	0.521
Hypertension (n)	11	8	7	0.551
Type 2 diabetes (n)	2	3	1	0.581
Education level (n)				0.826
Uneducated	4	6	6	
≤ 6 years	10	10	11	
7–12 years	10	7	7	
>12 years	6	6	5	
Onset frequency (n)	5.0±6.2	4.2±5.1	4.6±4.9	0.865
MMSE score*	21.8±3.5	20.7±3.5	21.0±3.0	0.456

\*MMSE: Mini-Mental State Examination scale, total score is 30 and a higher score indicates better cognitive function.

**Yizhi Xingnao prescription increased MoCA scores in MCI patients after TIA**

The cognitive function of patients was assessed at 30 and 60 days after drug treatments. Results showed that the MoCA score was significantly improved in the three groups of patients compared with before treatment ( $P < 0.01$ ). For each sub-scale of MoCA, scores of vision of space, execution function, naming, attention, language, abstract thinking, delayed recall and orientation were significantly increased after Yizhi Xingnao prescription treatment, compared with before treatment ( $P < 0.01$ ; Table 3); the scores of naming, attention, language, abstract thinking and delayed recall were significantly increased after ergoloid mesylates treatment ( $P < 0.01$ ; Table 4). There was no statistically significant difference of sub-scale scores in the control group before and after treatment ( $P > 0.05$ ; Table 5).

Table 2 Total score and sub-scale scores of Montreal Cognitive Assessment (MoCA) in the three groups before treatment

Group	n	MoCA total score	Vision of space and execution function	Naming	Attention	Language	Abstract thinking	Delayed recall	Orientation
Yizhi Xingnao prescription	30	18.50±3.96	3.77±1.25	1.27±0.83	4.20±1.52	1.37±0.76	0.97±0.72	2.67±1.21	4.27±1.36
Ergoloid mesylates	29	18.52±3.82	4.00±0.89	1.41±0.78	3.93±1.31	1.69±0.71	1.03±0.68	2.41±1.18	4.03±1.32
Control	29	18.76±3.47	3.66±1.26	1.69±0.97	3.93±1.65	1.69±0.76	1.24±0.69	2.93±1.28	3.62±1.50
F		0.043	0.683	1.825	0.319	1.850	1.237	1.293	1.615
P		0.958	0.508	0.167	0.728	0.163	0.295	0.280	0.205

MoCA total score is 30, a higher score indicates better cognitive function. Data are expressed as mean ± SD and there was no significant difference among groups following analysis of variance ( $P > 0.05$ ).

Table 3 Total score and sub-scale scores of Montreal Cognitive Assessment (MoCA) in Yizhi Xingnao prescription group (n = 29) before and after treatment

Time	MoCA total score	Vision of space and execution function	Naming	Attention	Language	Abstract thinking	Delayed recall	Orientation
Before treatment	18.52±4.03	3.72±1.25	1.31±0.81	4.17±1.54	1.38±0.78	0.97±0.73	2.72±1.19	4.24±1.38
30 days after treatment	22.34±3.12 <sup>a</sup>	4.14±0.92 <sup>a</sup>	1.93±0.65 <sup>a</sup>	4.66±1.14 <sup>a</sup>	2.00±0.65 <sup>a</sup>	1.41±0.63 <sup>a</sup>	3.55±1.09 <sup>a</sup>	4.66±1.08 <sup>a</sup>
60 days after treatment	25.59±2.20 <sup>a</sup>	4.41±0.73 <sup>a</sup>	2.38±0.56 <sup>a</sup>	5.03±1.02 <sup>a</sup>	2.45±0.63 <sup>a</sup>	1.72±0.45 <sup>a</sup>	4.34±0.94 <sup>a</sup>	5.24±0.95 <sup>a</sup>

Data are expressed as mean ± SD. <sup>a</sup> $P < 0.01$ , vs. before treatment (repeated measurements analysis of variance, pairwise comparisons using paired t-test).

Table 4 Total score and sub-scale scores of Montreal Cognitive Assessment (MoCA) in ergoloid mesylates group (n = 27) before and after treatment

Time	MoCA total score	Vision of space and execution function	Naming	Attention	Language	Abstract thinking	Delayed recall	Orientation
Before treatment	18.63±3.90	3.96±0.90	1.41±0.80	4.07±1.21	1.67±0.73	1.07±0.68	2.44±1.19	4.00±1.36
30 days after treatment	23.22±2.55 <sup>a</sup>	4.07±0.87	2.22±0.80 <sup>a</sup>	5.07±0.78 <sup>a</sup>	2.30±0.72 <sup>a</sup>	1.59±0.50 <sup>a</sup>	3.78±0.80 <sup>a</sup>	4.66±1.08
60 days after treatment	24.30±2.35 <sup>a</sup>	4.11±0.85	2.37±0.84 <sup>a</sup>	5.30±0.67 <sup>a</sup>	2.56±0.64 <sup>a</sup>	1.70±0.47 <sup>a</sup>	4.04±0.81 <sup>a</sup>	5.24±0.95

Data are expressed as mean ± SD. <sup>a</sup>P < 0.01, vs. before treatment (repeated measurements analysis of variance, pairwise comparisons using paired t-test).

Table 5 Total score and sub-scale scores of Montreal Cognitive Assessment (MoCA) in control group (n = 25) before and after treatment

Time	MoCA total score	Vision of space and execution function	Naming	Attention	Language	Abstract thinking	Delayed recall	Orientation
Before treatment	18.88±3.62	3.56±1.29	1.64±0.99	3.76±1.69	1.72±0.79	1.36±0.64	2.96±1.24	3.88±1.36
30 days after treatment	19.80±3.37 <sup>a</sup>	3.72±1.17	1.68±0.99	4.00±1.50	1.80±0.71	1.52±0.65	3.00±1.32	4.08±1.32
60 days after treatment	20.52±3.65 <sup>a</sup>	3.76±1.13	1.84±0.99	4.04±1.76	1.92±0.76	1.60±0.65	3.20±1.41	4.16±1.31

Data are expressed as mean ± SD. <sup>a</sup>P < 0.01, vs. before treatment (repeated measurements analysis of variance, pairwise comparisons using paired t-test).

After treatment for 30 days, the MoCA total scores after *Yizhi Xingnao* prescription or ergoloid mesylates treatment were significantly increased compared with the control group (P < 0.01), but there was no significant difference between the two groups (P > 0.05). After 60 days of treatment, the MoCA total score was higher in the *Yizhi Xingnao* prescription group than that in the ergoloid mesylates group and control group (P < 0.05 or P < 0.01; Figure 2).

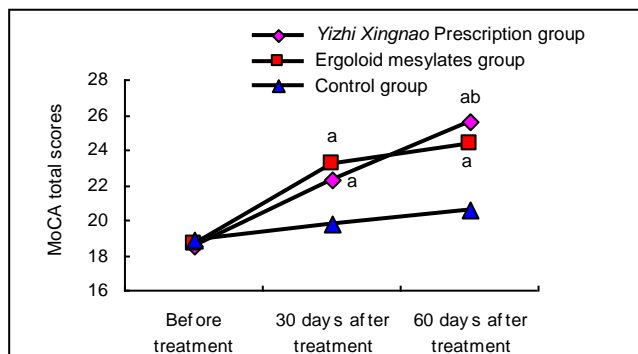


Figure 2 Comparison of Montreal Cognitive Assessment (MoCA) total scores in the three groups.

Data are expressed as mean ± SD. There were 29, 27, 25 patients in *Yizhi Xingnao* prescription group, ergoloid mesylates group and control group, respectively.

<sup>a</sup>P < 0.01, vs. control group; <sup>b</sup>P < 0.05, vs. ergoloid mesylates group (one-way analysis of variance, two groups were compared using the independent two-sample t-test).

### Yizhi Xingnao prescription treatment of patients with MCI

Analysis of the efficacy index showed that the effective rate and markedly effective rate were significantly increased after *Yizhi Xingnao* prescription or ergoloid mesylates treatment compared with the control group

(P < 0.01 or P < 0.05). These two indices were lower in the *Yizhi Xingnao* prescription group at 30 days after treatment, but higher at 60 days, compared with the ergoloid mesylates group. There was no statistically significant difference between the two groups at 30 and 60 days (P > 0.05; Table 6).

Table 6 Comparison of the efficient rate and markedly efficient rate [n (%)] in the three groups

Group	n	30 days after treatment	
		Efficient rate	Markedly efficient rate
Yizhi Xingnao prescription	29	12(41) <sup>b</sup>	6(21) <sup>b</sup>
Ergoloid mesylates	27	14(52) <sup>b</sup>	9(33) <sup>b</sup>
Control	25	3(12)	0
Group	n	60 days after treatment	
		Efficient rate	Markedly efficient rate
Yizhi Xingnao prescription	29	23(79) <sup>b</sup>	16(55) <sup>b</sup>
Ergoloid mesylates	27	17(63) <sup>a</sup>	11(41) <sup>a</sup>
Control	25	6(24)	2(8)

<sup>a</sup>P < 0.05, <sup>b</sup>P < 0.01, vs. control group (chi-square test of R × C table data).

### Adverse reactions

Three patients had loss of appetite and five patients appeared to have mild nausea after treatment with *Yizhi Xingnao* prescription. Four cases in each of the ergoloid mesylates group and control group showed mild nausea, which was then remitted by itself or by symptomatic treatment.

### DISCUSSION

TIA patients are associated with MCI regarding memory, language, attention, spatial perception, calculation, abstract thinking and reasoning, which are the preliminary

symptoms of dementia<sup>[13-16]</sup>. A timely and effective clinical intervention is important for preventing or delaying the occurrence of dementia. The MoCA scale has been widely applied to screen MCI in clinical practice<sup>[17-18]</sup>, is recognized as a reliable and valid means to assess many aspects of cognitive domains<sup>[19-22]</sup>, and is sensitive and specific for the determination of cognitive impairment after a TIA<sup>[23-24]</sup>. Therefore, the present study utilized the MoCA scale as an assessment tool for drug efficacy. Bakker *et al*<sup>[9]</sup> conducted a one-year follow-up on patients with cognitive impairment after a TIA suggesting that reducing the frequency of a recurrent TIA would help improve cognitive impairment in patients. Accordingly, the reduced frequency of a TIA is considered as a basic principle of treatment in this study. In accordance with the *Guidelines for the Management of Transient Ischemic Attack*, formulated by the U.S. National Stroke Association<sup>[12]</sup>, aspirin served as a basic treatment. In addition, *Yizhi Xingnao* prescription and ergoloid mesylates<sup>[25-27]</sup> were also administered, to compare and search for an optimal therapeutic scheme. Many Chinese herbs can be used as therapeutic ingredients, including *Radix Polygoni Multiflori*, *Salvia miltiorrhiza*, *Fructus Ligustri lucidi*, *fructus amomi amari*, *Rhizoma Acori Talarinowii*, *Radix Polygalae*, *Fructus Schisandrae*, honey-fried *Radix Astragali*, *Fructus Lycii*, *Semen Astragali complanati*, *Semen Cuscutae*, *Radix Angelicae Sinensis*, *Rhizoma Chuanxiong*, *Allolobophora caliginosa trapezoides*, and *Arisaema Cum Bile*. *Radix Polygoni Multiflori* can enhance hematogenesis, raise immunity and improve cognitive performance<sup>[28]</sup>. *Salvia miltiorrhiza* promotes tissue repair and regeneration<sup>[29]</sup>. *Fructus Ligustri lucidi* has a protective effect against chromosomal damage<sup>[30]</sup>. *Fructus amomi amari*, *Rhizoma Acori Talarinowii*, *Radix Polygalae*, and *Fructus Schisandrae* can activate the nervous system, restore intelligence, protect against cerebral injury and show anti-dementia effects<sup>[31-33]</sup>. Meanwhile, honey-fried *Radix Astragali*, *Fructus Lycii*, *Semen Cuscutae*, and *Radix Angelicae Sinensis* have anti-anoxic and anti-fatigue effects, and also improve one's ability to cope with stress<sup>[34-36]</sup>. *Salvia miltiorrhiza*, *Semen Astragali complanati* and *Allolobophora caliginosa trapezoides* have been shown to ameliorate the rate of hemorheology<sup>[37-38]</sup>. *Rhizoma Chuanxiong*, *Rhizoma Acori Talarinowii*, *Radix Polygalae*, and *Arisaema Cum Bile* have sedative and anti-convulsant effects<sup>[39-40]</sup>. *Radix Polygoni Multiflori*, *Radix Polygalae*, *Fructus Schisandrae*, honey-fried *Radix Astragali*, and *Fructus Lycii* contribute to promote metabolism and delay aging<sup>[41-42]</sup>. Moreover, combinations of the various above-mentioned herbs can improve cognitive impairment in TIA patients. Results from this study found that total scores from MoCA were significantly improved in all patients after treatment, indicating that any treatment using *Yizhi Xingnao* prescription, ergoloid mesylates and aspirin can improve cognitive function in patients after a TIA. As for cognitive domains (vision of space and execution

function, naming, attention, language, abstract thinking, delayed recall and orientation), the impairments were significantly improved after treatment with *Yizhi Xingnao* prescription, partially improved after treatment with ergoloid mesylates and no improvement was observed in the control group. This result is evidence that *Yizhi Xingnao* prescription has a broader range of improvement on cognitive functions than ergoloid mesylates. After 30 days of treatment, the MoCA total scores in the *Yizhi Xingnao* prescription and ergoloid mesylates groups were significantly higher than that in the control group, but there was no significant difference observed between the *Yizhi Xingnao* prescription group and the ergoloid mesylates group. At 60 days, the *Yizhi Xingnao* prescription group showed a significantly higher total score than the ergoloid mesylates group, indicating that *Yizhi Xingnao* prescription is not effective in early stages of treatment and gradually becomes superior to ergoloid mesylates. Analysis of the efficacy index showed that *Yizhi Xingnao* prescription and ergoloid mesylates were more effective than the control group, although there was no significant difference between the two. In summary, *Yizhi Xingnao* prescription is more effective than ergoloid mesylates or aspirin alone in the treatment of cognitive dysfunction after TIA, and no apparent adverse reactions are found. Thus it is a safe and effective decoction of traditional Chinese medicine that prevents or delays the occurrence of dementia.

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## SUBJECTS AND METHODS

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### Design

A randomized, controlled, clinical trial.

### Time and setting

Experiments were performed from January 2007 to February 2011 at the Third Affiliated Hospital of Nantong University, China.

### Subjects

Patients with MCI after a TIA were selected from the Third Affiliated Hospital of Nantong University, China between 2007 and 2010.

### Diagnosis and inclusive criteria

All patients met the diagnosis criteria revised by the Fourth Academic Conference of National Cerebrovascular Diseases<sup>[43]</sup> and the evaluative standards reported by Petersen *et al*<sup>[44]</sup>: complaints of loss of memory; memory impairment in verbal memory test; a clinical dementia rating of 0.5<sup>[45]</sup>; general cognitive function is normal and the Mini-Mental State Examination total score is more than the threshold value of dementia; ability to maintain normal daily life within 72 hours after the onset of a TIA; the duration from the first TIA attack to enrollment in the study ranged from 24 hours to 4 years; patients were normal by computed tomography or magnetic resonance imaging examination, with good visual acuity and hearing.

### Exclusion criteria

Patients with cerebral infarction, cerebral hemorrhage,

central nervous system infections, carbon monoxide or alcoholism encephalopathy, dementia, and history of mental illness were excluded.

All patients were informed of the whole research procedure before experimentation, and signed the informed consent form. In total, 88 patients that met the inclusion criteria were included in the study.

## Methods

### Drugs

*Yizhi Xingnao* prescription was produced by Jianguyin Tianjiang Pharmaceutical Co., Ltd. (Jianguyin City, China; lot No. 070928). Crude drugs in each pouch included *Radix Polygoni Multiflori* 10 g, honey-fried *Radix Astragali* 6 g, and 5 g of each *Salvia miltiorrhiza*, *Fructus Ligustri lucidi*, *fructus amomi amari*, *Rhizoma Acori Talarinowii*, *Fructus Lycii*, *Semen Astragali complanati*, *Semen Cuscutae*, *Radix Angelicae Sinensis*, *Rhizoma Chuanxiong*, *Allolobophora caliginosa trapezoides*, and *Arisaema Cum Bile*, as well as 3 g of each *Radix Polygalae* and *Fructus Schisandrae*.

### Administering drugs

All patients were orally administered with aspirin (100 mg × 30 tablets; Bayer, Leverkusen, Germany) anticoagulant therapy, 100 mg a day, for 60 consecutive days. Previous treatment can continue to treat underlying diseases (such as diabetes and hypertension), except some traditional Chinese medicines that can activate blood circulation and dissipate blood stasis. *Yizhi Xingnao* prescription group: patients were orally administered with *Yizhi Xingnao* prescription dissolved in warm water, twice per day for 60 consecutive days. Ergoloid mesylates group: patients were orally administered with ergoloid mesylates (1 mg; 50 tablets; Tianjin Huajin Pharmaceutical Ltd., Tianjin, China), twice per day for 60 successive days. The control group received no other drugs.

### Cognitive function in patients assessed by the MoCA scale

The cognitive function in patients was evaluated with the MoCA scale at 30 and 60 days after treatment. The MoCA scale comprised the visual space and executive function (cube, watch), naming, memory, attention, repeat sentences, verbal fluency, abstract thinking, delayed recall and orientation, conducted in an alternative connectivity test pattern. The total score of this scale was 30 and a higher total score indicated better cognitive function<sup>[18]</sup>. Patients who received less than 12 years of education were graded one more point, to correct for bias in education. All patients were assessed by two trained assessment staff by face-to-face measurement, and their consistency coefficient was 0.912.

### Evaluation of clinical efficacy

The clinical efficacy of the treatment was evaluated according to the Assessing Criteria for the Diagnosis, Dialectic and Curative Effect of Vascular Dementia, issued by Tian *et al*<sup>[46]</sup>. Marked efficacy: efficacy index ≥ 50%; advance (efficacy): efficacy index ≥ 20%;

ineffective: efficacy index < 20%. Efficacy index = (MoCA scores after treatment – MoCA scores before treatment) / MoCA scores before treatment × 100%.

### Statistical analysis

Quantitative data were expressed as mean ± SD and compared using SPSS 16.0 software (SPSS, Chicago, IL, USA). The average number of samples among multiple groups were compared by one-way analysis of variance, and comparisons between the two groups was done using the independent two-sample *t*-test; the average number of samples in groups at different times before and after treatment was compared with repeated measurements analysis of variance, and pairwise comparisons were conducted using the paired *t*-test; the rate difference of groups was compared with the R × C table data chi-square test. All testing was assumed as α = 0.05, and a level of *P* < 0.05 was considered statistically significant difference.

**Author contributions:** Donglin Jiang was responsible for the research, and had full access to data acquisition and integration, and wrote the manuscript. Xing Chu had full access to the study design and validation, revised the manuscript, and was the head of funds. Lingling Hu participated in the clinical research. Feng Hu was responsible for clinical research and statistical analysis. Junming Sun participated in the clinical research, provided technical and equipment support. Chengwan Li and Shengyang Jiang assisted in the literature review and some experimental operations.

**Conflicts of interest:** None declared.

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**Ethical approval:** The pilot study was given approval from the Ethics Committee at the Third Affiliated Hospital of Nantong University, China.

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