

## Original Research Article

# Clinical efficacy of idebenone in stroke patients with mild cognitive impairment, and its effect on regional homogeneity of resting-state functional magnetic resonance imaging of the brain

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### Abstract

**Purpose:** To evaluate the clinical efficacy of Idebenone in stroke patients with mild cognitive impairment, and its effect on regional homogeneity (ReHo) of resting-state functional magnetic resonance imaging (rs-fMRI) of the brain.

**Methods:** One hundred and twenty stroke patients with mild cognitive impairment who were admitted to the Department of Neurology of the China Rehabilitation Research Center Beijing Boai Hospital from January 2018 to January 2020 were enrolled in this study. The patients were randomly divided into control group and study group. Control group was treated with nimodipine, while the study group received a combination of nimodipine and idebenone.

**Results:** Clinical efficacy was higher in the study group than in the control group ( $p < 0.05$ ). Scores on Montreal cognitive assessment (MoCA), mini-mental state examination (MMSE), and activity of daily living scale (ADL) were significantly elevated ( $p < 0.05$ ) in both groups after treatment, but scores for MoCA and ADL were significantly higher in the study group than in the control group ( $p < 0.05$ ). After 6 months of treatment, there were significantly more patients with improved clinical dementia rating (CDR) in the study group than in the control group ( $p < 0.05$ ).

**Conclusion:** The use of idebenone and nimodipine for treatment of stroke patients with cognitive dysfunction leads to significant improvement in clinical outcomes, and enhancement of cognitive function and quality of life, due to improved brain function in the precuneus. However, the mechanism involved in the combination therapy-induced enhancement of cognitive function requires further investigation.

**Keywords:** Stroke, Cognitive dysfunction, Resting-state functional magnetic resonance imaging of brain, Regional homogeneity, Quality of life

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## INTRODUCTION

Cerebral stroke comprises ischemic and hemorrhagic stroke. It is also known as cerebrovascular accident, and it is an acute cerebrovascular disease in which brain tissue damage is triggered by sudden rupture of blood vessels in the brain, or insufficient blood flow to the brain due to vascular obstruction [1]. Stroke is characterized by high morbidity, mortality, and disability. It is a major cause of death in China, and a leading cause of disability in adults. Cognitive impairment is defined as an impairment in one or more of the cognitive functions which compromises daily or social activities [2]. Post-stroke cognitive impairment (PSCI), a common sequela of stroke, has an incidence of 27 % after the first onset of stroke, and it seriously undermines the survival of patients [3]. Studies have shown that 20 % of PSCI patients progressively develop dementia within 18 months, while 80 % of PSCI patients develop Alzheimer's disease within 6 years [4]. In addition, PSCI leads to emotional disorders such as anxiety and depression, and it increases the risk of falls which induce secondary strokes and life-threatening events, thereby imposing heavy burdens on families and society [5,6].

Nimodipine is a selective dihydropyridine calcium channel blocker which selectively dilates cerebral blood vessels. It reverses vasospasm, and significantly increases blood flow, thereby alleviating clinical symptoms in patients with vascular dementia [7]. In addition, nimodipine inhibits neuronal necrosis and apoptosis, stabilizes nerve cell function, and enhances learning and memory functions [8]. Idebenone, a bioengineered mimetic, is an effective antioxidant which inhibits lipid peroxidation, protects cell membranes and mitochondria from oxidative damage as a result of cellular metabolism, and prevents endogenous aging. It has been reported that idebenone facilitated ATP production by activating mitochondrial function and improving glucose utilization by the brain [9]. Moreover, it ameliorated brain metabolism of 5-hydroxytryptamine, and it exerted strong antioxidant and free radical scavenging effects [9]. Idebenone exerts a pro-intelligence effect by amelioration of cerebral dysfunction and brain dysfunction. To date, the use of combination of nimodipine and idebenone in the treatment of cognitive dysfunction after stroke, has not been reported [10]. Resting-state functional Magnetic Resonance Imaging (rs-fMRI) is a non-invasive functional imaging technique widely used in brain research. The technique aids in indirectly reflecting the neural activity of the brain by scanning and measuring deoxygenation and oxygen and hemoglobin levels in brain tissue. The rs-MRI is an invaluable method in the study

of human brain function. In recent years, rs-fMRI has been increasingly used in clinical basic research owing to advances in data analytical methods [11]. Regional homogeneity (ReHo), one of the analytical approaches used in rs-fMRI, effectively evaluates the regional activity of the human brain at rest [12]. Accordingly, in the present study, clinical efficacy of combination of nimodipine and idebenone in PSCI patients, and its effect on ReHo of Rs-fMRI, were investigated.

## METHODS

### Patients

A parallel, randomized controlled study design was used for this study. One hundred and twenty patients with stroke-induced mild cognitive impairment, who were hospitalized in the Department of Neurology of the China Rehabilitation Research Center Beijing Boai Hospital from January 2018 to January 2020, were selected and divided into a study group and a control group using the random number table method. There were 60 patients in each group. The study protocol was approved by the ethics committee of the China Rehabilitation Research Center Beijing Boai Hospital, and followed international guidelines for human studies. The patients voluntarily signed informed consent form before enrollment. Moreover, all patients voluntarily cooperated throughout the study period.

### Inclusion and exclusion criteria

#### *Inclusion criteria*

The included patients were: (a) those who met the diagnostic criteria for stroke and MCI; (b) patients with ischemic stroke confirmed by computed tomography or MRI, occurrence of cognitive impairment after cerebrovascular disease, and Hachinski ischemia scale score > 7 points [13] (excluding Alzheimer's disease); (c) patients with objective cognitive impairment, mini-mental state examination (MMSE) scale score of 21 - 26 points (elementary school education plus 1 point), and Montreal cognitive assessment (MoCA) scale score of 19 - 25 points [14]; (d) those with stable vital signs and consciousness, and (e) patients aged 40 - 80 years. There was no restriction on gender.

#### *Exclusion criteria*

Patients in the following categories were excluded from the study: (a) those with depression or severe organ damage such as cardiac insufficiency, liver, and kidney

dysfunction, or severe diabetes mellitus; (b) patients with impaired consciousness and inability to cooperate with the test; (c) those with moderate or severe cognitive impairment (MMSE score less than 21 points) after evaluation; (d) patients who were illiterate or had severe visual, hearing, and speech dysfunctions that would interfere with their cooperation during the study; (5) those who used any medications likely to affect cognitive function in the previous one month, or those who were undergoing other clinical trials; (f) patients with contraindications related to MRI; (g) those who had other medical histories that did not meet the inclusion criteria.

### **Treatments**

Control group was treated with nimodipine (Bayer HealthCare Co. Ltd., approval number: Guopharmachem H20003010; specification: 30 mg x 20 tablets) at a dose of 30 mg at a time, 3 times daily after meals. The study group was given liebenone (Shenzhen Haiwang Pharmaceutical Co. Ltd.; approval No: Guomao Zhizhi H10970363; specification: 30 mg x 12 tablets), 30 mg at a time and 3 times daily after meals, in addition to the treatment given to the control group. Patients in the two groups were treated for 6 months.

### **Rs-fMRI data management**

#### ***Pre-processing***

Before and after treatment, functional MRI data were acquired using 3.0T MRI (Signa Excite System, General Electric Medical Systems, Milwaukee, WI, USA). A total of 300 consecutive whole-brain functional scan (TR = 2s, TE = 30 ms, FOV = 240 mm, flip angle = 80°, matrix size = 64 × 64, thickness = 4 mm) resting-state images were collected. An eye mask was used to block the auditory and visual perceptions of each patient during scanning. Image scanning, temporal correction, head motion correction, spatial normalization, and spatial smoothing were performed using the methods described in the literature.

#### ***ReHo analysis***

The DPARSF Toolkit was used to perform ReHo analysis of the previously processed data. The ReHo analysis was done to extract signal changes in the time series of a given voxel, and to perform a similarity or consistency analysis with signal changes in the time series of its neighboring voxels. In this study, 26 adjacent voxels were identified, and the ReHo values were calculated for each voxel, centered on a

single voxel and its neighboring voxels, to obtain the ReHo maps for each voxel. The results obtained from the ReHo analysis were localized to brain regions and image presentation using MRICron software.

### **Assessment of treatment indicators/parameters**

#### ***MoCA score***

The MoCA scale was used for evaluating cognitive function. It had 14 parameters, including attention and concentration, visuospatial and executive function, abstract thinking, language, computational power, memory, and orientation, with a total score of 30 points. The higher the score, the better the cognitive function.

Based on degree of increase or decrease in MoCA score, clinical efficacy was categorized as markedly effective, effective, ineffective, or deteriorated. Treatments that led to increases in MoCA score of  $\geq 20\%$ ,  $\geq 12\%$  and  $< 12\%$ , relative to pre-treatment score, were considered as markedly effective, effective, and ineffective, respectively. However, if the treatment led to a decrease of  $> 12\%$  in MoCA score, relative to pre-treatment score, the patient's condition was considered to have deteriorated.

Treatment effectiveness was calculated as the sum of no. of markedly effective case and no. of effective cases, divided by total no of case, and expressed as a percentage. Change in MoCA score was computed as the difference between post-treatment score and pre-treatment score, divided by pre-treatment score, and expressed as a percentage.

#### ***MMSE score***

The MMSE usually consists of 10 items that measure orientation (time and place), memory (immediate and delayed memory), attentional computation, verbal ability (naming, retelling, listening comprehension, reading, and writing); and visuospatial ability. The higher the score, the better the cognitive function.

#### ***CDR score***

The clinical dementia rating (CDR) scale [15] was used for rapid assessment of the severity of a patient's condition by interviewing the patient and their families to obtain information necessary for assessment of cognitive level. The scores obtainable was 0, 0.5, 1, 2 and 3 points. A score of 0 point indicated normal condition, while

scores of 0.5, 1, 2 and 3 points indicated suspicious, mild, moderate, and severe clinical dementia, respectively. A decrease in score of  $\geq 1$  was considered as "improvement".

### Quality of life

Before and after treatment, the quality of life of each patient was assessed using the activity of daily living scale (ADL) [16]. This scale was used to assess ability of the patient to carry out daily physical activities associated with living. These included eating, dressing-up and grooming, telephoning, shopping and commuting.

### Follow up indicators

All patients were followed up every 4 weeks after drug administration, to monitor the occurrence of adverse events such as new cerebral hemorrhage, cerebral infarction, and other conditions. An adverse event record form was filled out, and the adverse events were classified into grades 1 - 4, where grade 1 indicated safety without any adverse reactions, grade 2 indicated relative safety with mild adverse reactions that did not require any treatment, grade 3 indicated moderate adverse reactions for which the treatment could be continued after proper management, while grade 4 indicated serious adverse reactions that required immediate termination of the treatment.

### Statistical analysis

The SPSS 22.0 software was used for statistical analysis of data. Measurement data are expressed as mean  $\pm$  standard deviation (SD). The *t*-test of two independent samples was used for comparison between groups, while *t*-test of

paired samples was used for comparison within groups at different times. Count data are expressed as numbers and percentages (n (%)), and were statistically analyzed using chi-square ( $\chi^2$ ) test. Differences were considered statistically significant at  $p < 0.05$ .

## RESULTS

### Baseline data

There were no significant differences between the two groups, with respect to gender, age, BMI, disease duration, and underlying disease ( $p > 0.05$ ). These data are presented in Table 1.

### Clinical efficacy

There were 21 markedly effective, 22 effective, 12 ineffective and 5 deteriorated cases in the study group, accounting for total treatment effectiveness of 71.67 % (43/60). In contrast, the control group had 29 markedly effective, 24 effective, 5 ineffective, and 2 deteriorated cases, with a total treatment effectiveness of 88.33 % (53/60). Statistical analysis showed that clinical efficacy was significantly better in the study group than in the control group ( $p = 0.023$ ; Table 2).

### MoCA scores

Before treatment, there was no significant difference in MoCA scores between the two groups ( $p > 0.05$ ). However, post-treatment MoCA scores were significantly increased in both groups, but with higher scores in the study group than in the control group ( $p < 0.05$ ). These results are presented in Figure 1.

**Table 1:** Comparison of baseline data

Parameter	Control group (n=60)	Study group (n=60)	t/ $\chi^2$	P-value
Age (years)	66.15 $\pm$ 11.05	61.95 $\pm$ 13.18	1.892	0.061
Gender (male/female)	41/19	38/22	0.333	0.564
BMI (kg/m <sup>2</sup> )	22.05 $\pm$ 1.85	21.49 $\pm$ 2.01	1.588	0.115
Course of disease (months)	7.59 $\pm$ 2.14	8.01 $\pm$ 2.49	0.991	0.324
<b>Underlying disease (n)</b>				
Hypertension	42	38	0.600	0.439
Diabetes	15	19	0.657	0.418
Hyperlipidemia	17	14		

**Table 2:** Comparison of clinical efficacy (n (%))

Group	Markedly effective	Effective	Ineffective	Deteriorated	Total efficacy
Control (n=60)	21 (35.00)	22 (36.67)	12 (20.00)	5 (8.33)	43 (71.67%)
Study (n=60)	29 (48.33)	24 (40.00)	5 (8.33)	2 (3.33)	53 (88.33%)
$\chi^2$					5.208
P-value					0.023

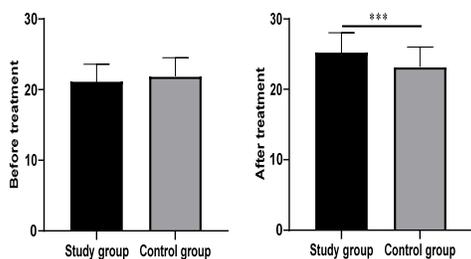


Figure 1: Comparison of MoCA scores; \*\*\* $p < 0.001$

**MMSE scores**

Before treatment, MMSE scores were similar in the two groups. However, although post-treatment MMSE scores were significantly elevated in the two groups, there was no statistically significant difference between the groups ( $p > 0.05$ ), as shown in Figure 2.

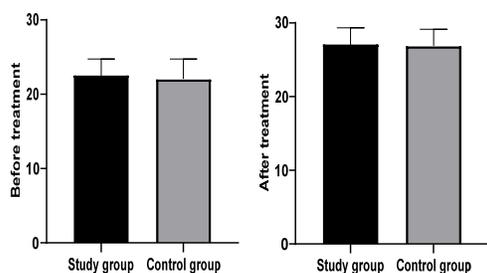


Figure 2: Comparison of MMSE scores

**CDR scores**

In the control group, 28 cases had improved CDR after 1 month of treatment, but after 2 and 6 months of treatment, the numbers of patients who had improved CDR scores rose to 34 and 42, respectively. In the study group, 31 patients

Table 3: Comparison of CDR scores (n, (%))

Group	1 month	3 months	6 months
Control (n=60)	28 (46.67)	34 (56.67)	42 (70.00)
Study (n=60)	31 (51.67)	42 (70.00)	53 (88.33)
$\chi^2$	0.300	2.297	6.114
P-value	0.584	0.130	0.013

had improved CDR scores after 1 month of treatment, while after 2 and 6 months, the numbers of patients who had improved CDR scores were 42 and 53, respectively. Thus, after 6 months of treatment, there were markedly higher number of patients with improved CDR in the study group than in the control group ( $p = 0.013$ ). These results are shown in Table 3.

**ADL scores**

There was no significant difference in ADL scores between the two groups before treatment ( $p > 0.05$ ). However, after treatment, there were marked increases in ADL scores in the two groups, but the study group had significantly higher scores than the control group ( $p < 0.05$ ), as shown in Figure 3.

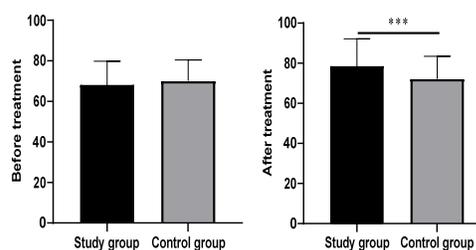


Figure 3: Comparison of ADL scores \*\*\* $P < 0.001$

**Distribution of brain regions with changes in ReHo values**

After treatment, the study group showed enhanced ReHo in the right insula, but ReHo was decreased in the left temporal lobe and middle right cingulate gyrus, when compared with the control group ( $p < 0.05$ ; Table 4).

Table 4: Comparison of distribution of brain regions with changes in ReHo values

Brain region	Peak point MNI coordinates			Voxel value	T
	X	Y	Z		
Middle right cingulate gyrus	8	-54	46	33	-3.58
Left temporal lobe	-9	-66	24	44	-4.65
Right insula	9	-46	32	36	4.28

**Table 5:** Comparison of incidence of adverse reactions (n, (%))

Group	Level 1	Level 2	Level 3	Level 4	Adverse reactions
Control (n = 60)	58	2	0	0	2 (3.33)
Study (n = 60)	56	3	1	0	4 (6.67)
$\chi^2$					0.702
P-value					0.402

### Incidence of adverse reactions

In the control group, there were 58 cases of safety level 1, and 2 cases of safety level 2, accounting for 3.33 % (2/60) incidence of adverse reactions. In contrast, the study group had 56 cases of safety level 1, 3 cases of safety level 2, and 1 case of safety level 3, accounting for 6.67 % (4/60) incidence of adverse reactions. There was no significant difference in the incidence of adverse reactions between the two groups ( $p < 0.05$ ). These results are presented in Table 5.

### DISCUSSION

In this study, the single therapy of nimodipine and the combined therapy of nimodipine and idebenone achieved positive results in patients with mild PSCI. However, the joint therapy outperformed the single therapy in terms of clinical efficacy, MoCA score, and ADL score. Cognitive impairment is a common complication of stroke. Approximately 80 % of patients with mild cognitive impairment develop Alzheimer's disease within 6 years. Alzheimer's disease seriously compromises the quality of life of the patient and leads to irreversible progression of the disease. This highlights the significance of early intervention in mild cognitive impairment after stroke [4].

Nimodipine is a dihydropyridine calcium channel blocker which selectively dilates cerebral blood vessels, reverses vasospasm, and remarkably increases blood flow. It is highly lipid-soluble, and it easily crosses the blood-brain barrier, resulting in better distribution of its bioactive form in the intracranial tissues than other calcium antagonists, as well as enhanced effect in the perivascular region of the brain. Previous research has shown that nimodipine produced significant differences between pre- and post-treatment temporal orientation, memory, calculation, and decision-making parameters in patients with mild PSCI, before and after treatment [17]. Cochrane used nimodipine at a dose of 90 mg/day for 12 - 24 weeks, produced a 39 % reduction in cognitive decline, with significant improvements in memory, attentiveness, orientation, and mood swings, thereby providing a rationale for the use of the drug [18].

Idebenone is an antioxidant which is a structural analogue of coenzyme Q10. However, its antioxidant activity is about 100 times higher than that of coenzyme Q10. It activates the respiratory activity of brain mitochondria, inhibits lipid peroxidation of mitochondria during brain ischemia and hypoxia, improves the energy metabolism of brain nerve cells, and enhances brain cell function. Indeed, the efficacy of idebenone in the treatment of cerebrovascular diseases is well-recognized. A study has demonstrated the efficacy of idebenone in the management of sequelae associated with cerebral infarction, cerebral hemorrhage, and cerebral arteriosclerosis which result in depression, low zest, affective disorders, and speech disorders [19]. In the present study, the pharmacological properties of nimodipine and idebenone were leveraged on to obtain enhanced clinical outcomes in patients with PSCI who were treated using a combination of the two drugs.

The technique of Rs-fMRI is used for spontaneous detection of neuronal activity in different brain regions in a resting state when the patient is quiet, supine and motionless, with eyes closed or open but not asleep, but without systematic thought activity. It establishes networks and functional connections between relevant brain regions, thereby reflecting spontaneous functional activity of the brain in the resting state.

Regional homogeneity (ReHo), a data processing method for regional brain functional activity, reflects the temporal synchronization of voxels with their neighbors in the whole brain, thereby enhancing localization of areas of discrepancy. It is used mainly for observing complex brain functional activity [20]. It has been revealed that ReHo values are highly correlated with cognitive function: increased ReHo values indicate that neuronal activity in local brain regions were temporally synchronized and cognitive function is relatively favorable [21]. In contrast, lowered ReHo values are consistent with reduced coherence of neuronal activity and impaired cognitive function [21].

Studies have demonstrated that post-stroke cognitive impairment in patients is closely related

to significantly reduced ReHo values in the bilateral anterior cingulate gyrus, left posterior cingulate gyrus and precuneus [22]. In the present study, ReHo was enhanced in the right insula, but it was decreased in the left temporal lobe and the middle right cingulate gyrus. Post-stroke cognitive impairment (PSCI) is a disease stage marked by presence of compensation and decompensation.

The results of this study showed that the ReHo values in the left cuneate lobe and right postcentral gyrus were reduced in the group given combined therapy, when compared with the group treated with monotherapy, whereas the ReHo values in the right insula were elevated. These results indicate that the combined treatment with nimodipine and idebenone significantly improved the overall cognitive level of PSCI patients, due to improvement of brain function in the precuneus [23].

## CONCLUSION

This study has demonstrated that the combination therapy of idebenone and nimodipine significantly improves clinical outcomes, and enhances cognitive function and quality of life of patients with stroke-induced cognitive dysfunction, due to improved brain function in the precuneus. However, the mechanism involved in the combination therapy-induced enhancement of cognitive function requires further investigation.

## DECLARATIONS

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### Funding

None provided.

### Ethical approval

None provided.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Conflict of Interest

No conflict of interest associated with this work.

## Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. All authors reviewed, read and approved the manuscript for publishing.

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