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*Original Article*

# Effect of citicoline adjuvant therapy on mild cognitive impairment in Parkinson's disease

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**Abstract:** To investigate the effect of citicoline adjuvant therapy on mild cognitive impairment (MCI) in Parkinson's disease (PD) (PD-MCI) and its influence on plasma phospholipid (PL) levels in PD-MCI patients. The demographic data on 81 PD-MCI patients among 185 idiopathic PD patients who participated in the research from November 2012 to December 2014 were collected, and which were randomly divided into a citicoline treatment group and a control group. Patients in the citicoline treatment group received citicoline sodium capsules orally (200 mg) three times daily (t.i.d.), in addition to the basic drug treatment. MoCA, SCOPA-COG evaluations and plasma PL level measurements were performed after 12 and 18 months of treatment. The MoCA and SCOPA-COG scores showed a significant difference between the treatment and control groups after 12 and 18 months of treatment ($P<0.05$, $P<0.01$), and the plasma PL levels in the treatment group, compared to the control group, significantly decreased after 12 and 18 months of treatment ($P<0.01$, $P<0.001$). Citicoline adjuvant therapy might delay the cognitive function decline rate in PD-MCI patients and reduce their plasma PL levels. Suggesting that this treatment has probablely neuroprotective effects.

**Keywords:** Parkinson's disease, mild cognitive impairment, phospholipids, citicoline, Montreal cognitive assessment, scales for outcomes in Parkinson's disease-cognition

## Introduction

Mild cognitive impairment (MCI) in Parkinson's disease (PD-MCI) is one of the main non-motor symptoms of Parkinson's disease (PD), with an incidence of approximately 20%-50% [1]. Effective treatment of PD-MCI are significant for improving PD patients' prognosis and quality of life, however, there is not effective treatment available up to now. Recent studies have found that Citicoline, a neuroprotective agent and membrane stabilizer, is often used in the adjuvant treatment of stroke, trauma and cognitive impairment [2]. Barrachina *et al*. [3] found that citicoline exhibits a neuroprotective effect in 6-hydroxydopamine-induced PD animal models. And more important, recent studies have shown that citicoline could increase brain dopamine levels and improve the cognitive impairment [4, 5], and it is well known that Phospholipids (PL), as major components of biological membranes, are crucial for maintaining cell membrane integrity and function. Hence we aims to examine the effect of citicoline adjuvant therapy on cognitive function and observe plasma PL level changes in PD-MCI patients to provide a basis for the early intervention of PD-MCI.

## Material and methods

### *Study subjects*

Idiopathic PD diagnosis refers to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria. PD-MCI diagnosis refers to the PD-MCI diagnostic criteria guide developed by the American Movement Disorder Society (MDS) [6]. Inclusion criteria for this study were as follows: (1) meeting UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria; (2) patients with a confirmed PD diagnosis and a gradual decline in cognitive function reported by the patients or people close to them or observed by clinical physicians; (3) cognitive

impairment confirmation based on formal neuropsychological testing; (4) cognitive impairment does not significantly interfere with functional independence, although it may introduce slight difficulty in performing complex functional tasks; and (5) evaluate mood status and visual hallucination to avoid confounding the evaluation of cognitive decline. Exclusion criteria for this study were as follows: (1) meeting Parkinson's disease dementia (PDD) diagnosis criteria proposed by the MDS special team; (2) other causes of cognitive impairment (such as delirium, stroke, severe depression, metabolic disorders, drug side effects and head trauma); and (3) PD-related co morbidities (such as movement disorders or severe anxiety, depression, excessive daytime sleepiness or mental disorders on the basis of MADRS, Hamilton).

According to the above inclusion and exclusion criteria, 81 PD-MCI patients among 185 idiopathic PD patients who participated in the research from November 2012 to December 2014 were included in this study; 46 were male, age 50-76 years old (mean 61.7 ± 8.9 y), course of disease from 4.5 years to 11 years (mean 7.5 ± 2.6 y); maximum education level was primary school and lower, secondary school, or college and higher education for 21 cases (25.9%), 40 cases (49.4%) and 20 cases (24.7%), respectively. All of the study subjects or their authorized family members signed informed consent forms, and the study protocol was approved by the Medical Ethics Committee of Weihai Municipal Hospital, Binzhou Medical College.

*Methods*

*Evaluation criteria:* The Unified Parkinson's Disease Rating Scale (UPDRS) III was used to assess the severity of motor symptoms in patients. The Chinese version of the Montreal Cognitive Assessment (MoCA) and Scales for Outcomes in Parkinson's disease-Cognition (SCOPA-COG) were used to assess mild cognitive impairment, including visual space, execution, naming, attention, language, abstract thinking, delayed recall and orientation ability. The SCOPA-COG includes 10 subtests subdivided into four sections: memory and learning, attention, executive functions, and visuospatial functions. The MoCA total score range is 0-30 points. If the subject has ≤12 years of education, 1 point is added to the test results to correct for the bias of education level. A patient with ≥26 points is considered normal, and a patient with 21-25 points is considered MCI [7]. The test time was approximately 10 minutes. The SCOPA-COG total scores is 43 points, with higher scores indicating better performances, a patient with 17-24 points is considered MCI, and the test took 10-15 minutes [8]. All of the assessment tests were performed by two assessment staff members with standardized training.

*Detection of plasma PL:* A 4 ml sample of fasting venous blood was taken from each patient. Before taking the blood, the patients were advised to avoid a high-fat diet and drinking. Patients were excluded from plasma PL measurements if they displayed the following conditions at the time of blood collection: fever, immunization, trauma, pregnancy or menstrual period. Whole blood was placed in a special anticoagulant tube (provided by Beijing Two fish Technology Development Co., Ltd.). The blood was centrifuged for 10 min (8000 r/min) to isolate platelet-poor plasma. The upper layer of platelet-poor plasma (1 ml) was used for PL measurements. Plasma PL was measured by chromatographic techniques combined with a modified inorganic phosphorus quantitative method. The result was presented in U. The measurement kit was purchased from Beijing Two fish Technology Development Co., Ltd. The kit instructions were strictly followed. The main steps were PL extraction, concentration, separation and color development. After incubation in a 90°C water bath for 5 min, the samples were cooled and equilibrated at room temperature for 35 min before measurement.

*Grouping and treatment:* According to the criteria, the patients were randomly divided into two groups by computer-generated randomization schedules, and blinding to group allocation was ensured. The control group received basic medications (L-dopa or pramipexole) with the matching placebo, while the combination therapy group took 200 mg citicoline sodium capsules given every 8 h (Sikaolin®, Qilu Pharmaceutical Co., Ltd.) orally on the basis of L-dopa or pramipexole treatment. After 12 and 18 months of treatment, the MoCA, SCOPA-COG assessment and PL levels were reexamined. The adverse effects of citicoline were not reported and no any cases in two groups were withdrawal.

**Table 1.** Baseline characteristics comparison between patients from treatment group and control group

| | Treatment group | Control group | *P* |
|---|---|---|---|
| Case number (%) | 41 (50.6%) | 40 (49.4%) | |
| Age at enrollment | 62.1 (54.1-72.8) | 61.8 (53.2-71.5) | 0.312 |
| Duration of disease | 7.5 (4.6-12.8) | 7.4 (4.5-11.0) | 0.816 |
| UPDRS III scores | 19.6 (6.2-24.5) | 20.4 (10.3-23.7) | 0.575 |
| Male/Female | 24/17 | 23/17 | 0.913 |
| Education years | 11.8 ± 7. 49 | 11.6 ± 8.15 | 0.495 |
| Using levodopa (%) | 56.6% | 55.8% | 0.852 |
| Mean daily levodopa dosage (mg) | 562.3 ± 18.5 | 555.5 ± 16.8 | 0.754 |
| Using receptor agonist (%) | 42.9% | 44.1% | 0.763 |
| Mean daily pramipexole dosage (mg) | 1.23 ± 0.23 | 1.30 ± 0.27 | 0.673 |
| MoCA score | 24.03 ± 3.22 | 23.89 ± 2.27 | 0.586 |
| SCOPA-COG score | 23.79 ± 2.82 | 23.43 ± 2.19 | 0.710 |

**Table 2.** MoCA scale score comparison between the two groups ($\bar{x}$ ± s)

| Group | *n* | Baseline MoCA | 12 months MoCA | 18 months MoCA |
|---|---|---|---|---|
| Treatment group | 41 | 24.03 ± 3.22 | 23.65 ± 2.55▲ | 23.12 ± 2.82△ |
| Control group | 40 | 23.89 ± 2.27 | 22.53 ± 4.14 | 21.49 ± 3.99 |

Compared to the control group ▲*P*<0.05; △*P*<0.01.

**Table 3.** SCOPA-COG scale score comparison between the two groups ($\bar{x}$ ± s)

| Group | *n* | Baseline SCOPA-COG | 12 months SCOPA-COG | 18 months SCOPA-COG |
|---|---|---|---|---|
| Treatment group | 41 | 23.79 ± 2.82 | 21.55 ± 3.05▲ | 21.09 ± 2.78△ |
| Control group | 40 | 23.43 ± 2.19 | 20.73 ± 4.14 | 19.25 ± 3.68 |

Compared to the control group ▲*P*<0.05; △*P*<0.01.

*Statistical methods*

SPSS18.0 statistical software was used for analysis. Quantitative data are shown as the mean ± standard deviation ($\bar{x}$ ± s). Student's t-test, analysis of variance or chi-square analysis was used to compare means of discrete and continuous variables. Comparisons among multiple groups were performed using one-way ANOVA; the 95% CI and OR value were calculated by Woolf statistical software. *P*<0.05 was considered statistically significant.

## Results

*Among the 185 PD patients, 81 (48.2%) had MCI (PD-MCI)*

These 81 PD-MCI cases were randomly divided into 2 groups: the treatment group (41 cases) and the control group (40 cases). The baseline demographic characteristics of the patients in the 2 groups are shown in **Table 1**.

*MoCA scale score comparison between the two groups*

The baseline MoCA scale scores of the treatment group and the control group showed no significant difference (*P*>0.05). After 12 months of treatment, the MoCA scale scores of the treatment group were significantly higher than those of the control group (*P*<0.05); after 18 months of treatment, the MoCA scale scores of the treatment group were significantly higher than those of the control group (*P*<0.01) (**Table 2**).

*SCOPA-COG scale score comparison between the two groups*

The baseline SCOPA-COG scale scores of the treatment group and the control group showed no significant difference (*P*>0.05). After 12 months of treatment, the SCOPA-COG scale scores of the treatment group were significantly higher than those of the control group (*P*<0.05); after 18 months of treatment, the SCOPA-COG scale scores of the treatment group were significantly higher than those of the control group (*P*<0.01) (**Table 3**).

*Plasma PL level comparison between the two groups*

The baseline plasma PL levels showed no significant difference in the treatment and control groups (*P*>0.05). After 12 months of treatment, PLs levels in the treatment group were significantly lower than those in the control group (*P*<0.01); after 18 months of treatment, PL lev-

**Table 4.** Plasma PL level (U) comparison between the two groups ($\bar{x} \pm s$)

| Group | *n* | Base PLs | 12 months PLs | 18 months PLs |
|---|---|---|---|---|
| Treatment group | 41 | 6.83 ± 0.65 | 5.22 ± 0.76* | 4.99 ± 0.84▼ |
| Control group | 40 | 6.77 ± 0.77 | 6.89 ± 0.91 | 7.10 ± 0.77 |

Compared to the control group, *$P$<0.01; ▼$P$<0.001.

els in the treatment group were significantly lower than those in the control group ($P$<0.001) (**Table 4**).

## Discussion

PLs are the major component of cell membranes. Membrane PLs in the central nervous system (CNS) are rich in polyunsaturated fatty acids (PUFAs). PUFAs metabolism is mainly controlled by phospholipase $A_2$ ($PLA_2$) and acyltransferase, *i.e.,* the so called "deacylation-reacylation cycle". Under normal conditions, released free fatty acids (FFA) under the effect of $PLA_2$ are rapidly taken up by membrane PLs. $PLA_2$ mainly acts on lipoproteins and the acyl bond at the *sn-2* position of glycerophospholipids in the cell membrane, releasing FFA and lysophosphatidic acid [9].

Citicoline, a nucleoside derivative, is the intermediate in membrane phospholipid biosynthesis. Exogenous citicoline is hydrolyzed to cytidine and choline to be absorbed. The resynthesis of citicoline is through cytidine triphosphate (CTP)-choline-phosphate cytidylytransferase, which is a phosphatidylcholine synthesis rate-limiting enzyme. Citicoline is a choline donor in acetylcholine biosynthesis. Studies have shown that citicoline has neuroprotective effects on cerebral ischemia, traumatic brain injury and memory disorders and addictive disorders; in addition, citicoline has good drug safety and tolerability [10-12]. In accordance with the above results, our results have shown that combination therapy with citicoline could delay the decline of cognitive function in PD-MCI patients, suggesting that citicoline might has protective effects on PD-MCI patients. However, the results of citicoline protective effect were inconsistent. Recently, a study has found that citicoline is not efficacious in the treatment of moderate-to-severe acute ischaemic stroke [13]. The precise reasons of the observed differences of these results were not completed clear, the possible reason were that in the ICTUS trial, they had more severe strokes and a ceiling effect resulting from an already maximal improvement due to rt-PA use, and different illness and the reasons for stroke in different races were not ruled out.

As an endogenous nucleoside donor, citicoline is mainly involved in three metabolic processes in the body [14]: (1) synthesis of phosphatidylcholine (lecithin), which is the major PL component of the cell membrane: (2) supply of choline for acetylcholine synthesis and for the regulation of the utilization efficiency of choline; and (3) oxidation of betaine, which is an important methyl donor. The major hydrolysis products of citicoline, choline and cytidine, are easily absorbed in the intestine and can cross the blood-brain barrier. Animal experiments have demonstrated [4] that citicoline can increase dopamine release, improve animal learning and memory function and improve the cognitive impairment caused by hypoperfusion in ischemia rats. What is more, in cocaine-addicted individuals, citicoline has been shown to increase brain dopamine levels and reduce cravings [5], suggesting that the possible role of Citicoline as dopaminergic modulator over cognitive functioning in PD. Silveri *et al*. [15] reported that after taking citicoline for 6 weeks, frontal lobe (anterior cingulate cortex) phosphatidylinositol, β-nucleoside triphosphate and the ratio of phosphoinositide to inorganic phosphate significantly increased in elderly individuals. In addition, citicoline can significantly increase membrane PL content, protect damaged cell membranes by accelerating phospholipid re-synthesis and improve cell ischemic injury by inhibiting the release of FFA. The study found that citicoline can antagonize the neurotoxic effects induced by iron overload [14].

Our study showed an obvious reduction in the MoCA and SCOPA-COG scale score for PD-MCI patients after 18 months of placebo treatment compare to the citicoline adjuvant therapy, suggesting that citicoline can delay the progression of cognitive impairment in PD-MCI patients. Our study found that for PD-MCI patients, plasma PL levels significantly decreased after 18 months of citicoline adjuvant therapy, suggesting that citicoline can increase PL synthesis and reuse, reduce the release of PL in the CNS

and offer neuroprotective effects. During the 18 months treatment and observation period of the treatment group, drug tolerance was good, except for a few patients who exhibited mild gastrointestinal reactions and excitement. No patients dropped out from the study, demonstrating the good safety of the drug.

The neuroprotective effect of citicoline is considered to be related to the following factors [2, 16-18]: (1) reducing FFA release; (2) increasing the synthesis of phosphatidylcholine and maintaining the normal structure and function of cardiolipin and sphingomyelin; (3) increasing glutathione and glutathione reductase activity and exerting an antioxidant effect; (4) restoring mitochondrial ATPase and cell membrane $Na^+$/$K^+$-ATPase activity and improving energy metabolism; (5) exerting anti-apoptotic effects; (6) providing anti-excitotoxicity; (7) increasing the synthesis and release of neurotransmitters, such as dopamine, acetylcholine and phosphoinositide, and improving cognitive function; and (8) repairing or increasing membrane PLs to accelerate the resynthesis of PLs. However, the exact mechanisms still require further study.

## Conclusion

In summary, our data suggest that PL metabolism disorder plays an important role in the molecular pathology of cognitive impairment in PD patients. Citicoline, as an important neuroprotective agent and membrane stabilizer, can delay the progression of cognitive impairment in PD-MCI patients; increase PL synthesis and re-use; and reduce PL release in CNS, thus providing neuroprotective effects in multiple ways. Because our study has a relatively small sample size, the long-term effect of citicoline and the effects of different citicoline doses on PD-MCI still require further in-depth study.

## Disclosure of conflict of interest

None.

## Abbreviations

MCI, mild cognitive impairment; PD-MCI, mild cognitive impairment in Parkinson's disease; PL, phospholipid; MDS, Movement Disorder Society; PDD, Parkinson's disease dementia; UPDRS, The Unified Parkinson's Disease Rating Scale; MoCA, the Montreal Cognitive Assessment; SCOPA-COG, Scales for Outcomes in Parkinson's disease-Cognition; CNS, central nervous system; PUFAs, polyunsaturated fatty acids; $PLA_2$, phospholipase $A_2$; FFA, free fatty acids; CTP, cytidine triphosphate.

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