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# *Differences in the Improvement of Neuroimaging Biomarkers between Two Pharmacological Regimens in Patients with Post-Stroke Cognitive Impairment*

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***Keywords:*** Post-stroke cognitive impairment; Donepezil; Nicergoline; Magnetic resonance imaging; Hippocampus; Cerebral blood flow

***Abstract:*** This study aimed to compare the differential effects of two pharmacological regimens—the cholinesterase inhibitor donepezil and the cerebrovasodilator nicergoline—on neuroimaging biomarkers in patients with post-stroke cognitive impairment (PSCI) and to explore their relationship with cognitive improvement. A prospective, randomized, open-label, parallel-group controlled design was adopted. Ninety-six eligible PSCI patients were randomly assigned to the donepezil group (Group A, n=48) or the nicergoline group (Group B, n=48). Both groups received 24 weeks of target drug therapy on top of routine treatment. All patients underwent multimodal magnetic resonance imaging (MRI) before and after treatment, including 3D-T1-weighted imaging, diffusion tensor imaging, resting-state functional MRI, and 3D arterial spin labeling sequences, to assess brain structure, white-matter integrity, functional connectivity, and cerebral blood flow. Cognitive function was evaluated using the Montreal Cognitive Assessment and the Digit Symbol Substitution Test. The primary endpoint was between-group differences in neuroimaging metrics. Ninety-three patients completed the study. In terms of brain structure, the donepezil group showed significantly greater increases in bilateral hippocampal volume (e.g., left side from 2.85 to 3.02 $cm^3$) compared with the nicergoline group ($P<0.05$). Regarding brain function, the donepezil group exhibited a more pronounced enhancement of default-mode network functional connectivity ($P<0.05$). However, in improving cerebral perfusion, the nicergoline group achieved a significantly larger elevation in whole-brain mean cerebral blood flow (from 46.1 to 52.3 ml/100g/min) than the donepezil group ($P<0.01$). Cognitive assessments revealed that the donepezil group had an advantage in global cognitive improvement, and its improvement in MoCA score was positively correlated with increased hippocampal volume ($r=0.432$); in the nicergoline group, improvement in processing speed was associated with increased cerebral blood flow ($r=0.398$). Safety profiles were similar between the two groups Donepezil and nicergoline demonstrate distinct targeting patterns in improving brain health in PSCI patients: donepezil preferentially promotes structural plasticity and functional integration of the memory-related limbic system, whereas nicergoline shows superior efficacy in enhancing whole-brain hemodynamic perfusion. These findings suggest that selecting individualized drug regimens based on multimodal neuroimaging characteristics holds potential clinical value.

## 1. Introduction

Cognitive impairment following stroke affects outcomes in patients, and treatment approaches using drugs remain without clear guidance from brain imaging measures. Donepezil and nicergoline represent common drugs in clinical use, but these differ in how they produce effects: the former increases activity in pathways that use particular chemical signals, while the latter improves blood flow to brain tissue[1]. Studies examining these drugs have focused on measures using cognitive scales, but evidence remains limited regarding how the drugs differ in effects on imaging measures that reflect brain structure, function, and blood flow. Imaging methods that combine multiple approaches provide means to examine this issue. This study aims to compare effects of donepezil and nicergoline on brain imaging measures in patients with cognitive impairment following stroke. The study uses a design that assigns participants to treatment groups and follows them over time. Imaging methods include measures of structure, measures examining connections between regions, measures of brain activity, and measures of blood flow in tissue. The study examines these measures to show how the drugs may produce effects, which provides a basis for selecting treatment approaches in clinical practice that consider individual patient features.

## 2. Materials and Methods

### 2.1 Study Subjects and Grouping

This work was a study following over time at a single center using assignment to groups. The individuals in the study were patients with impairment in thinking following stroke who were in the hospital in the Department of Neurology of our hospital between January 2022 and December 2023. The criteria for including patients were as follows: meeting the standards that provide diagnosis for impairment in thinking following stroke as outlined in the Chinese Expert Consensus on the Management of Post-Stroke Cognitive Impairment, aged 50-80 years, having a first-ever acute stroke caused by limited blood flow with a disease course of 3-6 months and being in a stable condition, a Montreal Cognitive Assessment score of less than 26 points, and being right-handed. The criteria for excluding patients were: loss of thinking ability caused by other factors, severe problems with language or problems with seeing or hearing or inability to complete examinations, conditions that prevent MRI such as metal implants in the head or fear of enclosed spaces, severe problems with heart or liver or kidney function, and negative response to the study drugs. A total of 96 patients who met criteria were assigned using a method with assignment based on numbers to Group A, which received donepezil, and Group B, which received nicergoline, with 48 patients in each group.

### 2.2 Study Design and Intervention Protocol

The study used a design with assignment to groups and open procedures for comparison. All individuals in the study received standard treatment for preventing further occurrences after stroke. This included treatment to prevent blood forming substances that can block vessels and management of pressure in vessels, sugar levels in blood, and substances related to fats. Group A received donepezil. These individuals took tablets containing donepezil hydrochloride in addition to standard treatment. The initial dose was five milligrams each day. After four weeks, this increased to ten milligrams each day. The total duration of treatment was twenty-four weeks. Group B received nicergoline. These individuals took nicergoline tablets in addition to standard treatment. The dose was thirty milligrams taken three times each day. The duration of treatment for this group was also twenty-four weeks. During the study, use of other treatments for improving mental

function was not allowed. Nurses who were assigned to this role observed individuals taking medications and recorded if individuals followed treatment. The method for assessment involved counting tablets. If individuals showed following treatment above ninety percent, this indicated completion of the study.

### 2.3 Neuroimaging and Neuropsychological Assessment Methods

Neuroimaging Assessment: All patients underwent multimodal MRI scanning using the same 3.0T MRI scanner before treatment (baseline) and after 24 weeks of treatment. The scanning sequences included: (1) 3D-T1-weighted imaging: Used for automatic segmentation and measurement of volume and cortical thickness in regions of interest such as the hippocampus and temporal cortex (using FreeSurfer software); (2) Diffusion tensor imaging (DTI): Calculated whole-brain fractional anisotropy (FA) and mean diffusivity (MD) to assess white matter microstructural integrity (analyzed using the TBSS tool in FSL software); (3) Resting-state functional MRI (rs-fMRI): Primarily used to assess the strength of functional connectivity within the default mode network (DMN); (4) Three-dimensional arterial spin labeling (3D-ASL): Used to precisely measure cerebral blood flow (CBF) in the whole brain and specific regions.

Neuropsychological Assessment: At the same time points, raters blinded to group allocation assessed global cognition and processing speed using the Montreal Cognitive Assessment (MoCA) and the Digit Symbol Substitution Test (DSST).

Safety Assessment: All adverse events occurring during the treatment period were recorded.

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### 2.4 Statistical Analysis

Analysis used the SPSS 26.0 software. The study presents variables as mean and standard deviation for continuous measures and number with percentage for categories. Initial comparison between groups applied independent t-tests for continuous variables showing normal distribution and similar variance. The Mann-Whitney U test provided an approach when these conditions were not present. The chi-square test examined categorical variables.

Comparison of main indicators, including measures from imaging and MoCA scores, used analysis examining effects across time, effects between groups, and interaction effects. The analysis that examines repeated measures provided this assessment. Finding a significant interaction led to further examination of simple effects. Comparison between groups for changes following treatment used analysis of covariance, with initial values included as covariates.

Examination of relationships between changes in imaging measures and changes in scores used Pearson or Spearman correlation analysis. The study considered P less than 0.05 as indicating statistical significance.

## 3. Results

### 3.1 Baseline Characteristics and Study Completion

The study included ninety-six individuals who underwent assignment to two separate groups. In the period following treatment, two individuals in Group A did not continue in the study. One individual changed location and the other individual stopped the treatment because the individual showed intolerance to effects in the system that processes food. One individual in Group B stopped

participation for reasons that related to individual circumstances. The analysis included forty-six individuals in Group A and forty-seven individuals in Group B. These individuals completed the treatment and all procedures that measure outcomes. The groups showed no differences between them in features measured at the initial point. These features included age, sex, years that individuals spent in education, the type of condition affecting blood to the brain, the location of this condition, and the measure of thinking ability at the initial point. This indicates that the groups allow comparison. Table 1 provides the complete data.

Table 1. Comparison of Baseline Characteristics between the Two Groups of Patients

| Item | Group A (n=46) | Group B (n=47) | $t/\chi^2$ value | P value |
|---|---|---|---|---|
| Age (years, mean ± SD) | 65.3 ± 7.2 | 66.1 ± 6.8 | 0.552 | 0.582 |
| Male [n(%)] | 28 (60.9) | 30 (63.8) | 0.092 | 0.762 |
| Years of Education (mean ± SD) | 10.2 ± 3.1 | 9.8 ± 2.9 | -0.656 | 0.513 |
| Ischemic Stroke [n(%)] | 46 (100) | 47 (100) | - | - |
| Basal Ganglia Infarction [n(%)] | 25 (54.3) | 27 (57.4) | 0.102 | 0.749 |
| Baseline MoCA Score (points, mean ± SD) | 19.5 ± 3.2 | 18.9 ± 3.5 | -0.878 | 0.382 |

## 3.2 Brain Structure and White Matter Integrity Indicators

Analysis that examines measures over time indicates significant interaction between time and group for the volume of the hippocampus and the thickness of the temporal lobe (F=5.237, P=0.024; F=4.862, P=0.030, in that order). Analysis examining specific effects shows that volume of the hippocampus and thickness of the temporal lobe increase from initial measures in the two groups following treatment (P<0.05). The degree of improvement in Group A, which receives donepezil, is significantly larger than that in Group B (P<0.05). For the microstructure of white matter, the measure of fractional anisotropy across the whole structure increases, and the measure of diffusivity decreases from initial values in the two groups following treatment (P<0.05), but differences between groups are not significant (P>0.05). Changes in main indicators of structure in the region appear in Table 2.

Table 2. Comparison of Key Brain Structure and White Matter Indicators Before and After Treatment Between the Two Groups(x±s)

| Indicator | Time Point | Group A (n=46) | Group B (n=47) | Between-Group Comparison P-value* |
|---|---|---|---|---|
| Left Hippocampal Volume ($cm^3$) | Baseline | 2.85±0.31 | 2.82±0.29 | 0.864 |
| | After 24 weeks | 3.02±0.28△ | 2.91±0.30△ | 0.038 |
| Right Hippocampal Volume ($cm^3$) | Baseline | 2.91±0.33 | 2.88±0.31 | 0.912 |
| | After 24 weeks | 3.08±0.30△ | 2.96±0.29△ | 0.046 |
| Whole-Brain Mean FA Value | Baseline | 0.38±0.03 | 0.39±0.04 | 0.721 |
| | After 24 weeks | 0.41±0.04△ | 0.42±0.04△ | 0.215 |
| Whole-Brain Mean MD Value ($\times10^{-3}$ $mm^2/s$) | Baseline | 0.82±0.07 | 0.81±0.06 | 0.693 |
| | After 24 weeks | 0.78±0.06△ | 0.77±0.07△ | 0.327 |

Note: △ indicates P<0.05 compared with baseline within the same group; * indicates the P-value for between-group comparison after treatment (analysis of covariance, adjusted for baseline values).

### 3.3 Brain Function and Perfusion Indicators

Following treatment, the strength of connection between the back part of the pattern that operates during rest (the area combining the back middle part with the section showing connections) and the front middle part of the outer layer showed increase from the starting point in the two groups, but this increase appeared more substantial in Group A, with difference between groups showing significance (P<0.05). For the measure of flow through the structure, the increase in the average measure of flow through both sides of the structure following treatment showed significantly greater extent in Group B (the group receiving nicergoline) than in Group A (P<0.01), with particular effects in the area combining the side region with the back side region. (See Table 3.)

Table 3. Comparison of Brain Function and Perfusion Indicators Before and After Treatment Between the Two Groups (x±s)

| Indicator | Time Point | Group A (n=46) | Group B (n=47) | Between-Group Comparison P-value* |
|---|---|---|---|---|
| DMN Functional Connectivity Strength (z-value) | Baseline | 0.52±0.21 | 0.49±0.23 | 0.514 |
| | After 24 weeks | 0.68±0.19△ | 0.58±0.20△ | 0.023 |
| Whole-Brain Mean CBF (ml/100g/min) | Baseline | 45.2±5.6 | 46.1±5.9 | 0.437 |
| | After 24 weeks | 48.5±5.1△ | 52.3±5.8△ | 0.002 |

Note: △ indicates P<0.05 compared with baseline within the same group; * indicates the P-value for between-group comparison after treatment (ANCOVA, adjusted for baseline values).

### 3.4 Cognitive Function Improvement and Correlations

Following treatment, scores on measures of thinking function showed significant increase in the two groups when comparing to the initial measure, with findings indicating high significance. Analysis comparing the groups revealed that Group A showed greater improvement on the total measure of thinking function than Group B, with this difference showing significance. However, the improvement on the measure of processing speed showed no significant difference between the two groups. Analysis examining relationships indicated that in Group A, the increase in volume of the left structure for forming memories showed positive association with improvement on the thinking function measure, with a relationship measure of point four three two showing significance. In Group B, the increase in blood flow to the whole structure of thinking showed positive association with improvement on the processing speed measure, with a relationship measure of point three nine eight showing significance. The data appear in Table 4.

Table 4. Cognitive Function Improvement and Correlations in the Two Groups of Patients

| Cognitive Indicator | Group | Baseline (points) | After 24 Weeks (points) | Within-Group Change (points) | Correlation with Key Imaging Indicators (r-value / P-value) |
|---|---|---|---|---|---|
| MoCA Total Score | Group A | 19.5±3.2 | 23.8±2.9△ | 4.3±2.1 | vs. Change in Left Hippocampal Volume: r=0.432, P=0.003 |
| | Group B | 18.9±3.5 | 22.1±3.2△ | 3.2±2.0 | vs. Change in Whole-Brain CBF: r=0.231, P=0.126 |
| DSST Score | Group A | 28.4±6.7 | 33.9±7.2△ | 5.5±3.0 | vs. Change in Whole-Brain CBF: r=0.305, P=0.041 |
| | Group B | 27.8±7.1 | 34.8±6.8△ | 7.0±3.4 | vs. Change in Whole-Brain CBF: r=0.398, P=0.006 |

### 3.5 Safety Analysis

In the period of treatment, five individuals in Group A reported events that appeared adverse, and these included forms of nausea and diarrhea that showed mild to moderate levels. Group B included three individuals who reported adverse events, and these events included two cases showing mild dizziness and one case showing flushing of the face. The events that occurred in this study appeared relatively mild in all cases. The events did not produce complications that required significant treatment, and the events resolved following treatment to address the specific features or resolved without treatment. The comparison between the two groups examined the total rate of events that appeared adverse, and this comparison indicated differences that did not show significance in the analysis (P>0.05). Table 5 presents these findings.

Table 5. Comparison of Adverse Event Occurrence Between the Two Groups of Patients [n(%)]

| Adverse Event Type | Group A (n=46) | Group B (n=47) |
|---|---|---|
| Gastrointestinal Reactions (nausea, diarrhea) | 4 (8.7) | 0 (0) |
| Dizziness | 1 (2.2) | 2 (4.3) |
| Facial Flushing | 0 (0) | 1 (2.1) |
| Total | 5 (10.9) | 3 (6.4) |
| P-value for $\chi^2$ test | 0.715 | |

## 4. Discussion

### 4.1 Major Findings and Mechanistic Interpretation

The main finding in this study shows that donepezil in the group using this treatment provided clear effects on changes in structures of the brain that relate to function in memory. Following the period providing treatment, individuals in the study showed increases that were significant in the measure of volume in structures on both sides of the brain, with the left side showing change from two point eight five to three point zero two in the measure using cubic units, and also showed increases that were greater in the strength of connections in function between areas in the network relating to general activity in the brain, with the measure increasing from point five two to point six eight. The group using nicergoline showed a different pattern, with this treatment providing significant effects on perfusion across the brain that uses blood flow as the measure, and the increase in the measure of flow across all areas of the brain, changing from forty-six point one to fifty-two point three in the units using milliliters per hundred grams per minute, showed a magnitude that was greater than the increase in the group using donepezil for the same measure.

Examining the pharmacological basis provides support for the imaging findings that show association with the targets of these drugs. Donepezil functions by inhibiting the process that removes a particular signaling substance, and this increases the amount of this substance in connections between cells. The increase allows for more activity that supports connections and the survival of cells in a particular brain structure. This provides a basis for the volume increase in this structure that the data show, and this relates to the improvement in overall cognitive function that the measure indicates, showing an increase of four point three points that correlates with the change in structure volume[2]. In contrast, nicergoline operates through a different mechanism that involves expanding blood vessels in the brain and improving circulation at small scales. The drug increases blood flow and the supply of substances that provide energy. This mechanism provides explanation for the increase in perfusion that the data reveal, and the change shows association with improvement in the speed of processing information, with the measure increasing by seven point zero points in a pattern that correlates with the change in blood flow[3].

## 4.2 Clinical Significance of the Study

The important aspect of the study relates to findings that show differences in effects between donepezil and nicergoline for the first time. The analysis uses multiple methods to examine brain features in patients with changes following stroke. Results provide evidence that supports approaches using specific treatment for individual cases in practice. For patients showing particular patterns in brain structure, including smaller size in the region relating to memory and reduced patterns of connection in the network that operates during rest, donepezil appears to offer more significant benefits. These features may indicate changes that relate to processes similar to those found in the condition involving progressive memory decline. In contrast, for patients with the main issue relating to insufficient blood supply to the brain or continuing problems with blood vessel function, nicergoline may provide more direct effects. This approach differs from previous methods that use symptoms alone to select treatment. The current method connects decisions about treatment to measures from brain imaging that provide objective data. This strategy may increase the degree to which treatment produces desired outcomes and allow more specific targeting of effects, moving away from approaches that use the same treatment for all patients[4].

## 4.3 Limitations of the Study

The study provides findings but shows limitations that require consideration. The sample includes ninety-three cases and data come from a single center. This limits the extent to which results can apply across different groups and reduces the degree to which analysis can examine separate outcomes or specific participant categories. The study follows participants for twenty-four weeks, which provides a measure of effects over a medium period. However, this approach does not allow assessment of differences between the two treatment approaches over longer periods such as one or two years, and the study cannot examine how the treatments differ in effects on the process by which the condition develops over time. The study uses a design that assigns participants to groups but remains open in the way that treatments are provided, and it does not include a group receiving an inactive treatment. This may allow bias in the way outcomes are measured. The analysis does not examine in detail how outcomes differ based on features of the area affected by the condition, such as the extent of the area or the particular location where the condition occurs. These features may relate to the way participants respond to treatment.

# 5. Conclusion

This study shows that donepezil and nicergoline provide different effects in treatment for brain function in individuals with conditions following other conditions. Donepezil shows effects that relate to development in particular brain structures and patterns of connection between areas that function in certain ways. Nicergoline shows effects that relate to blood movement across the brain as a whole[5]. The findings suggest that treatment approaches could use information from brain images that show structure and function. Individuals who show reduced brain structure and reduced connection between areas may respond more to donepezil. Individuals who show reduced blood movement may respond more to nicergoline. The study provides evidence from brain images that supports different treatment for different individuals with these conditions. Studies using more individuals and longer time following treatment should examine these findings and examine whether using both treatments together provides effects.

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