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P300 latency changes in patients with mild cognitive impairment after taking choline alphoscerate; A preliminary study

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ABSTRACT

Choline alphoscerate in clinical studies improved cognitive dysfunction in dementia, but it did not show any clear clinical benefit on mild cognitive impairment (MCI). There is limited evidence of neuropsychological markers in showing the effects of cholinergic precursors in MCI. Object of this preliminary study is to evaluate the change of the P300 latency as a biomarker for cognitive function after taking choline alphoscerate in patients with MCI. Event related evoked potential study were done in baseline (n = 27) and 3 months after taking choline alphoscerate (n = 17). When compared to our previous reported control database, the difference of the P300 latencies between MCI and control group at baseline was statistically significant ($P < 0.01$). Although Follow-up P300 latencies after taking choline alphoscerate did not show the significant change, the tendency of shortened P300 latencies was identified. Even though there are some limitations, choline alphoscerate could improve the electrophysiological markers in MCI patients. To identify the effect of cholinergic precursor in MCI and the usefulness of electrophysiological biomarkers, well-designed further study is needed.

1. Introduction

Mild cognitive impairment (MCI) interposes between dementia and cognitively normal state [1,2]. Differentiation of MCI from dementia depends on their function, how it impaired in daily activities. MCI has relatively higher chance to progress to dementia, 10–15% per year, when compare to cognitively normal elders over 65, 1–2% [3]. The treatment of MCI has not established yet. The evidence of cholinesterase inhibitors, donepezil, galantine and rivastigmine, or cholinergic precursors in MCI is insufficient [4]. Considering Alzheimer's disease present clinical symptoms mainly due to cholinergic deficit, cholinergic precursors are one of the strategies to enhance the cholinergic system. Choline alphoscerate compose choline and glycerol-1-phosphate, and its choline is used for production of acetylcholine and glycerol-1-phosphate for phospholipid, substrate for damaged cell membrane [5]. Some preclinical studies have shown the efficacies in enhancing learning and memory. A clinical study, ASCOMALVA (Association between the Cholinesterase Inhibitor Donepezil and the Cholinergic Precursor Choline Alphoscerate in Alzheimer's Disease), showed that it enhances and elongates the effectiveness when taking with donepezil on Alzheimer's disease with cerebral ischemia [6]. However, there has been few clinical evidence in prescribing it in MCI [7].

P300 of an event related evoked potentials reflect a processing speed of neurons, which could be used as a biomarker for cognitive function [8]. P300 is late positive electrical potential elaborated at 300 ms after subject is differentiating target and non-target stimulation. Its generator has not been known, but hippocampus, amygdala, thalamus and basal ganglia are supposed [9]. It could be used as a measuring tool of cognitive dysfunction in many neurological disorders, and it is especially related to attention and short-term memory. It reflects an early cognitive change in MCI and predicts dementia in elderly Alzheimer's disease [10,11].

Our hypothesis is that choline alphoscerate could improve the cognition of MCI subjects, which could be reflected in electrophysiological biomarkers like P300 potential. The object of this study is to evaluate changes of P300 latencies in MCI after taking choline alphoscerate for 3 months.

2. Subjects and methods

2.1. Subjects

We studied 34 subjects older than 50 and under 85 years, comprising all with amnestic form mild cognitive impairment (MCI). All

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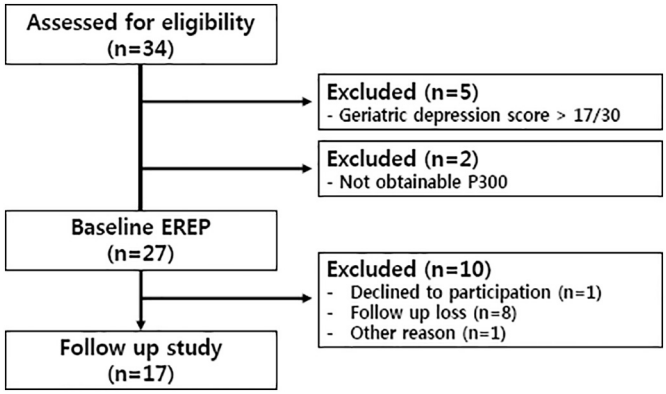

Fig. 1. Enrollment of the subjects.

patients with MCI met the following guidelines based on the criteria proposed by Petersen: 1) subjective memory complaint, 2) normal general cognitive function as defined by scores on the Korean version of the Mini-Mental State Examination (K-MMSE) ≥ -1.0 standard deviation of the norms for age- and education-matched normal subjects, 3) normal activities of daily living (ADL), as judged both clinically and on the ADL scale described below, 4) objective cognitive impairment on at least one of the four domains of comprehensive neuropsychological tests with scores below the 16th percentile, and 5) not demented [12]. Patients with neurological or psychiatric illnesses such as stroke, schizophrenia, epilepsy, and encephalitis and patients with geriatric depression scale (GDpS) > 17/30 were excluded. There was no subject taking sleep pills or anti-depressants. We got informed consents from 34 MCI patients, including 5 patients who have GDpS > 17/30 and 2 patients not obtainable P300 potential. A total of 27 patients with aMCI participated in baseline study. Of the 27 eligible patients in the study, 10 patients were excluded in follow up study: one because of decline of participation, eight because of follow-up loss and one because of poor drug compliance < 70% (Fig. 1). The design and protocol of this prospective study were approved by the Institutional Review Board of our hospital (registration no. C2010050).

2.2. Measures

Routine laboratory examinations for dementia assessment, including B12 and folate serum levels, serology for syphilis, dosage of thyroid hormones and MRI were carried out in all patients. MCI in our clinic is a diagnosis carried out by trained neurologists using a standardized mental status battery, and it includes K-MMSE, Clinical Dementia Rating (CDR) and CDR Sum of Boxes (CDR-SOB), Hachinski ischemia scale, and Geriatric depression scale (GDpS). All participants underwent a standardized neuropsychological battery known as the Seoul Neuropsychological Screening Battery [13].

2.3. Recording of P300

We used the oddball paradigm included two different sounds, 1000 Hz non-target and 2000 Hz target stimulus. The stimuli were presented to both ears with 70 dB and target stimuli were randomly generated in 20% of non-target stimuli. The stimulation rate was 0.97/s and the total number of stimulation was 200, which was averaging to get P300 wave. The subjects were seated with the eye closed and directed to count the target stimulation in mind to get attention to target stimulation. During the test, subjects were warned not to move their eye balls.

Electrodes were applied Fz on the international 10–20 system as an active, A1 + 2 on mastoid process as a standard FPz as a ground electrode with resistance below 5 Kohm The sweep speed was 50 ms/div; high filter was 70 Hz, and low filter was 1 Hz. P300 potential latency was measured in peak of the wave that the most prominent positive wave located between 250 and 800 ms.

2.4. Statistical analysis

Values were expressed as mean ± SD. The results of this research were statistically analyzed using R. Base-line P300 latencies of 27 patients were compared to the 38 normal control subjects who was previously studied by authors [14]. The *t*-test was applied to identify significant age differences and 'generalized linear model' procedure was applied in order to prove the difference of the P300 latencies between the MCI patients and cognitively normal subjects after controlling with age. The spearman correlation analysis was used to assess relationship between age and P300 latency in each group. Statistical significance was fixed at $P < 0.05$.

After base-line P300, patients had taken choline alphoscerate 400 mg twice a day for 3 months. And then follow-up P300 was done within 7 days. Finally, 17 subjects were analyzed because of 1 for withdrawal of the consent, 8 for follow-up loss and 1 for poor drug compliance. The base-line P300 latencies were compared to the latencies after taking choline alphoscerate using paired *t*-test. Statistical significance was fixed at $P < 0.05$.

3. Results

3.1. Baseline study

The baseline P300 latency of controls from our database was 304.76 ± 33.02 ms, and MCI was 324.74 ± 38.88 ms, and the difference of the P300 latencies was statistically significant ($P < 0.01$). There was a significant age difference between control (n = 38, 62.4 ± 7.0) and MCI (n = 27, 70.2 ± 8.3) group. The latency of MCI was prolonged (generalized linear model, corrected by age, $P < 0.01$) (Table 1) and did not show any linear correlation with age (rho = 0.12, $P = 0.51$) in contrast that control significantly did (rho = 0.56, $P < 0.01$) (Fig. 2).

3.2. Follow up study

Of the 27 MCI subjects, only 17 finally could be analyzed to evaluate choline alphoscerate effect on the electrophysiological change. P300 latencies of MCI (n = 17, 69.8 ± 6.4 years) after taking choline alphoscerate for 3 months (313.2 ± 31.6 ms) were shortened to compare to baseline (321.5 ± 38.2 ms) but not significant (paired *t*-test, $P = 0.190$). However, Fig. 3 showed the tendencies of the latency changes, where the dots below the line (Y = X) represents that follow-up latencies were shortened.

Table 1
Age and P300 latencies, mild cognitive impairment (MCI) patients and control subjects. The difference of the P300 latencies controlled with age between the MCI patients and control subjects was statistically significant ($P < 0.01$).

	N	Age*	P300 latency†	R**
		Mean ± SD	Mean ± SD	
Control	38	62.4 ± 7.0	304.76 ± 33.02	0.62
MCI	27	70.2 ± 8.3	324.74 ± 38.88	0.15
Total	65	58.25 ± 10.75	313.06 ± 36.74	

N, number of subject; R, Pearson correlation coefficient.

* $P < 0.01$, Statistical significance test was done by *t*-test.

† $P < 0.01$, Statistical significance test was done by GLM procedure. Evaluated at covariates appeared in the model: Age = 65.63.

** Correlation is significant at the 0.01 level (2-tailed).

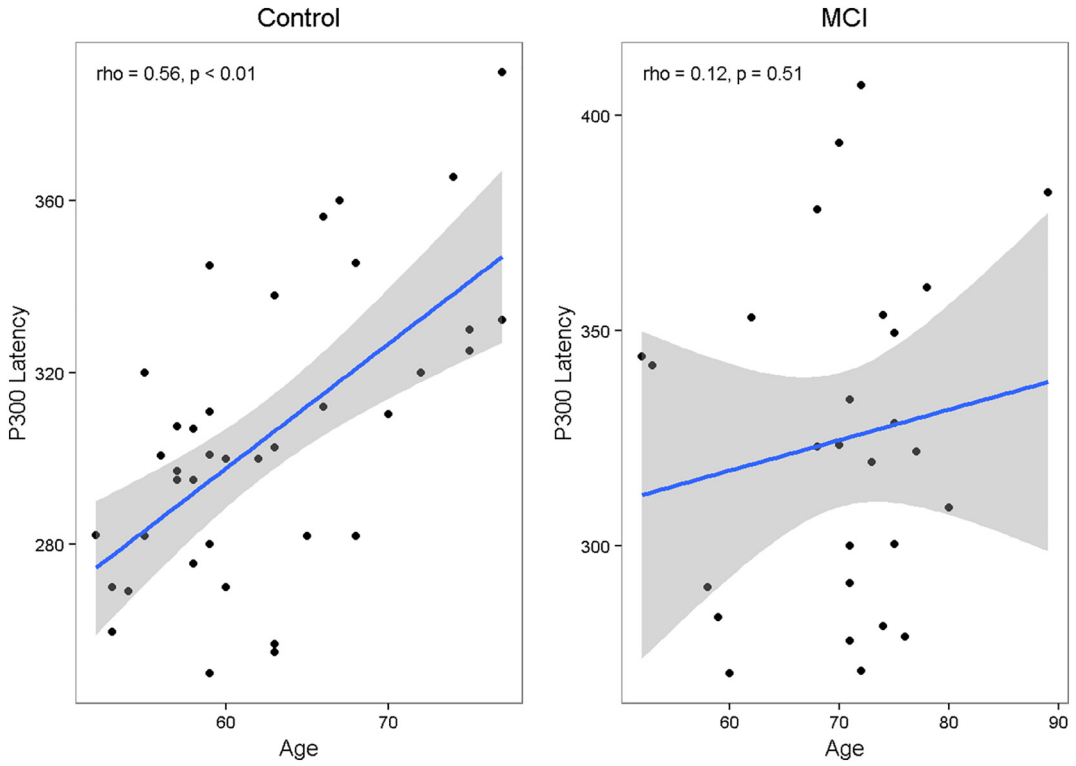

Fig. 2. P300 latency distributions of control and mild cognitive impairment subjects according to age. The latency of P300 in patients with mild cognitive impairment losses the linear relationship to age.

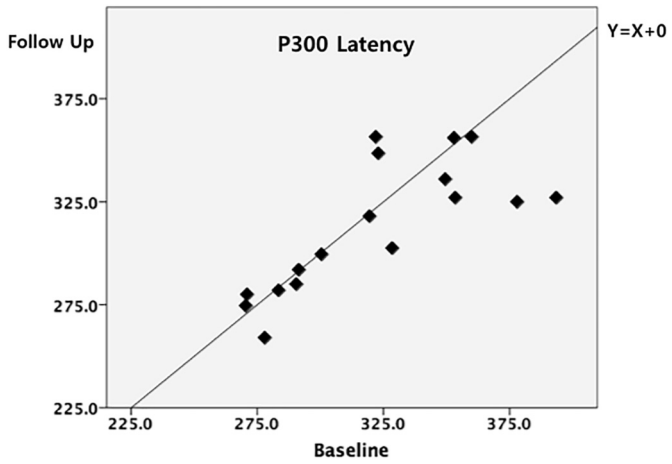

Fig. 3. The P300 latencies at baseline and follow up studies in patients with mild cognitive impairment. The dots below the line (Y = X + 0) represent shortened P300 latencies of MCI patients in the follow up studies after taking choline alphoscerate.

4. Discussion

First finding in this study was that MCI showed delayed P300 latency and loss of linear relationship with age. The P300 latency is thought to reflect cognitive processes in stimulation categorization [8], and it also involved in attention and short-term memory [15]. Previous researches presented prolonged P300 latency in patients with degenerative dementia and mild cognitive impairment [10,11]. Cognitive impairment rate is significantly correlated to the latency value [15]. P300 latencies of healthy persons are the shortest in early 3rd decades and then delayed with age [16]. Cognitive impairment in MCI elongates the P300 latency, and it changes the linear relationship with ages [10,11,15,16]. So we theorized that P300 could be a monitoring biomarker for drug effect, especially on cognitive function.

Our second finding is that although MCI subjects taking choline alphoscerate for 3 months did not show the significant electrophysiological improving, the tendency of shortened P300 latencies was identified. Most clinical studies to evaluate the effects of nootropics on MCI are failed [4]. One of the reasons was that they used neuropsychological indicators to represent the change of cognitive function [4]. Most of the neuropsychological markers are not delicate to evaluate the drug effect on MCI subjects [4], and some drugs did not receive the credit even though they already had real value in MCI. Choline alphoscerate is one of the drugs. Many clinicians prescribe it in cognitive impairment, but clinical evidence supporting its effectiveness on MCI is poor [7]. However, the improving tendency of P300 latencies after taking choline alphoscerate in our study suggested the possibility of cognitive improvement. The enrollment of larger population will give the statistical evidence.

The current study was subject to some limitations. Our data were obtained from a small number of patients, which could lead to ambiguous statistical findings in direct comparisons. Although no significant changes in P300 latencies were observed after taking choline alfoscerate, the tendency of shortened P300 latencies was identified. Therefore, a larger patient cohort could more robustly identify differences. To this end, the enrollment of additional participants is currently ongoing. Additionally, we did not verify the cognitive improvement by neuropsychological tools. Another our limitation is that this study was not a randomized control study, furthermore, showed too high drop-out rate.

Even though many limitations, this is a preliminary study to suggest the possibility of choline alphoscerate effect on aMCI and P300 as electrophysiological marker to monitor drug effects on cognitive impairment. However, further studies, like a randomized control study, are needed to evaluate the precise choline alphoscerate effect, and the interest on electrophysiological markers is also required to make up neuropsychological markers to monitor drug effect.

Author contributions

Dr. Su-Hyun Han: first author, drafting/revising the manusctipt for content, Dr. Hae-Bong Jeong: review the manuscript, Dr. Kwang-Yeol Park: statistical analysis, critique of the manuscript and study supervision, Hae-Won Shin and SangYun Kim: revising the manusctipt for content. Dr. Young Chul Youn: corresponding author, analysis or interpretation of data, study supervision.

Conflict of interest

None declared.

Financial disclosure

There are no conflicts of interest. The authors report no disclosures.

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