Huperzine-A response to cognitive impairment and task switching deficits in patients with Alzheimer’s disease

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Abstract
Background: Alzheimer’s Disease (AD) is associated with cognitive decline due to various pathological mechanisms. There are several acetylcholinesterase inhibitor compounds which can improve cognition, but Huperzine-A is a natural sesquiterpene alkaloid extracted from Chinese herb (Huperzia Serrata) which has rapid action.
Methods: Double blind study was conducted. Participants included 50 patients with AD and 50 healthy individuals. Patients were recruited from Civil and BV hospital Bahawalpur and Nishter hospital Multan, Pakistan during May 2017 until February 2018 who were stable on Huperzine-A medication. Patients were tested twice. First, at the time of diagnosis to determine baseline scores. Second, post eight weeks of Huperzine-A treatment. Healthy individuals had single testing session. Participants completed Addenbrooke’s Cognitive Examination and Trail Making Test.
Results: Patients with AD showed cognitive and task switching deficits in contrast with healthy individuals. There was significant improvement in cognition and task switching abilities post Huperzine-A treatment compared with baseline performance.
Conclusion: Huperzine-A is effective in reducing cognitive and task switching deficits in patients with AD.
Keywords: Acetylcholinesterase inhibitor; Alzheimer’s disease; Cognition; Huperzine-A

1. INTRODUCTION
Alzheimer’s Disease (AD) is a progressive neurodegenerative disorder characterized by irreversible brain damage affecting cognitive, behavioral and emotional functioning of individuals eventually leading to death due to complete brain failure. There are 46.8 million people living with AD and dementia around the world. This number would increase up to 131.5 million people by the year 2050.1 Initial symptoms include cognitive decline and memory impairment which extend toward behavioral anomalies as the disease progress.2 Cognitive impairment involves several pathological mechanisms such as presence of neurofibrillary tangles and neuritic plaques in frontal, temporal, parietal, occipital lobes and limbic cortex,3 lesions of the cerebral cortex deteriorating interconnections between cortical-subcortical areas through proteinaceous intraneuron spread,4 atypical immunoreactivity of phosphorylated tau in neocortical neurons,5 enlarged deposits of positive reactive microglia (HLA-DR) in substantia nigra and abridged cortical activity of choline acetyltransferase,6 inclusions of brain alpha-synuclein positive,7 accumulation of iron in neurofibrillary tangles and senile plaques contributes in the formation of oxygen radicals and inducing oxidative stress.8,9 Cognitive impairment in executive function, language, visuospatial function, episodic and semantic memory are related with tau pathology (as measured by 18F-AV-1451 binding in temporal, fronto-parietal, occipitotemporal brain regions) and grey matter atrophy (11C-PiB uptake) observed through positron emission tomography.10 Loss of frontal and parietal synaptic density is considered as a major correlate of cognitive impairment in AD.11 Number of neurofibrillary tangles in entorhinal cortex, area 9 and CA1 are predictors of cognitive impairment.12 Demyelinations of subcortical white matter and periventricular area are determinants of cognitive decline in AD.13 Huperzine-A is a natural sesquiterpene alkaloid compound extracted from Huperzia Serrata (Chinese herb) which acts as a reversible acetylcholinesterase (enzyme that break downs acetylcholine) inhibitor by crossing blood-brain barriers. Huperzine-A as a dietary supplement is efficacious in improving cognitive status and activities of daily living in patients with AD.14 Huperzine-A is an alkaloid with neuroprotective properties. Animal studies have demonstrated that Huperzine-A acts as protective agent countering organophosphate (OP) intoxication eventually reducing glutamate-induced cell death.15 Huperzine-A has stronger penetration in blood brain barrier, prolonged duration of acetylcholinesterase inhibitory action and greater bioavailability than other cholinesterase inhibitors (donepezil, rivastigmine, and tacrine). Huperzine-A has cognitive enhancing properties by protecting against several pathological factors inducing neurodegeneration such as beta-amyloid protein (or peptide), ischemia, hydrogen peroxide, glutamate, apoptosis and staurosporine-induced cytotoxicity. As a result, oxidative stress is reduced, expression of apoptotic proteins (Bcl-2, Bax, P53, caspase-3) gets regulated, protection
of mitochondria and interference with amyloid precursor protein metabolism occurs, nerve growth factor and its receptors is up-regulated. Pharmacological studies have shown that Huperzine-A goes beyond inhibition of acetylcholinesterase, it can improve learning and memory deficits both in animal models and patients with AD. Twelve to eight week use of Huperzine-A can improve mental status as assessed through Mini Mental State Examination. Twelve week use of Huperzine-A significantly improved cognition, behavior, activities of daily living, and mood in AD patients. Task switching is an higher order executive function which rely on fronto-parietal network. Research has shown that patients with AD have task switching deficits. Such deficits cannot be improved with practice in AD patients. These patients were deficient in inhibition, cognitive flexibility, self-monitoring and attentional control, However, there is still a gap in literature to understand whether huperzine-A is efficacious in improving task switching deficits and major cognitive domains (memory, language, attention/orientation, fluency, visuo-spatial function). It was hypothesized that (i) Patients with AD would show cognitive and task switching deficits in contrast with healthy individuals (ii) Huperzine-A would significantly improve cognitive and task switching deficits in AD patients.

2. METHODS

Fifty patients diagnosed with AD according to DSM-5 at Civil and BV hospital Bahawalpur, and Nishter hospital Multan, Pakistan during May 2017 until February 2018 participated in the study. The inclusion criterion for patient group were as follows: (i) age above 50 (ii) mild/moderate dementia screened in the study. Th e inclusion criterion for patient group were: (i) having normal cognition (ii) non AD dementia. Fifty healthy individuals took part in the study. Inclusion criterion were: (i) physical and psychiatric disorder other than AD (ii) non AD dementia. Fifty healthy individuals took part in the study. Inclusion criterion were: (i) having normal cognition MMSE-score 24-30 (ii) no depression-score 0-9 (Table 1).

3. RESULTS

Statistical analysis was conducted through SPSS (version 20). Data on demographic variables showed that patients with AD were not different from healthy individuals on age and socio economic status. Sample had equal ratio of male and female (Table 1).

3.1. Baseline scores of patients with AD versus healthy individuals

Repeated measures analysis of variance (ANOVA) on scores of ACE with factors (AD patients’ baseline versus healthy individuals; within subject) revealed significant difference of scores between both subject groups on F (1, 49) = 1607.39, p < 0.001, 0.97. Patients with AD (79.96 ± 3.38) showed lesser scores than healthy individuals (98.54 ± 3.11). ANOVA on reaction times (sec) of TMT-A with factors (AD patients’ baseline versus healthy individuals) revealed significant difference of scores between both subject groups on F (1, 49) = 7472.41, p < 0.001, 0.99. Patients with AD were slower (110.66 ± 6.57) to perform TMT-A than healthy individuals (19.92 ± 2.66). Likewise, AD patients (269.62 ± 25.47) were slower than healthy individuals (75.50 ± 2.90) to perform TMT-B.

Table 1: Characteristics of sample (n = 100).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AD Group (n = 50)</th>
<th>Control Group (n = 50)</th>
<th>t (df), p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (54–75 years)</td>
<td>64.36 ± 5.18</td>
<td>63.66 ± 5.75</td>
<td>t(49) = 0.71, p = 0.47</td>
</tr>
<tr>
<td>Gender (male: female)</td>
<td>25:25</td>
<td>25:25</td>
<td></td>
</tr>
<tr>
<td>Education (11–16 years)</td>
<td>13.02 ± 1.42</td>
<td>12.96 ± 1.32</td>
<td>t(49) = 0.20, p = 0.84</td>
</tr>
<tr>
<td>Disease duration (1–4 years)</td>
<td>2.60 ± 1.06</td>
<td>1.28 ± 0.78</td>
<td></td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease.

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had deteriorated functioning on daily activities in contrast with healthy individuals (7.96 ± 0.19), $F(1, 49) = 3324.96$, $p < 0.001$, 0.98 (Table 2).

3.2. Baseline versus post Huperzine-A treatment scores of patients with AD

Repeated measures ANOVA on scores of Patients with AD on ACE with factors (baseline versus post-treatment; within subject) showed post-treatment significant increase in scores (87.82 ± 1.32) compared with baseline performance (79.96 ± 3.38), $F(1, 49) = 1927.36$, $p < 0.001$, 0.97. ANOVA within subject factors (baseline versus post-treatment) showed significant decrease in reaction times post- Huperzine-A treatment of AD patients (baseline versus post-treatment 110.66 ± 6.57 versus 67.08 ± 9.57), $F(1, 49) = 1464.42$, $p < 0.001$, 0.96. Post-treatment (2.48 ± 0.99) scores showed improved functioning on instrumental daily activities compared with baseline scores (1.28 ± 0.78), $F(1, 49) = 147.00$, $p < 0.001$, 0.75 (Table 2).

3.3. Dementia severity and difference of scores between baseline and post Huperzine-A treatment

One way ANOVA was conducted to see pre and post Huperzine-A treatment differences on scores of ACE and TMT with dementia severity (mild vs. moderate) as fixed factor. Result showed that Huperzine-A treatment was equally effective for mild and moderate dementia groups ACE $F(1, 49) = 1.27$, $p = 0.26$, mild (7.32 ± 3.77) moderate (8.40 ± 2.92), TMT-A $F(1, 49) = 0.26$, $p = 0.61$, mild (91.28 ± 8.79) moderate (90.20 ± 5.88), TMT-B $F(1, 49) = 2.93$, $p = 0.09$, mild (119.76 ± 22.80) moderate (130.76 ± 22.59) (Table 3).

### 4. DISCUSSION

The present study was designed to assess efficacy of Huperzine-A on cognition and task switching. The study yielded several important results: (i) patients with AD showed deficient performance in various cognitive domains in contrast with healthy individuals (ii) AD patients were slower to perform visual attention and switching tasks compared with healthy individuals. In contrast, healthy individuals showed efficient performance on both parts of TMT (iii) After eight weeks of Huperzine-A treatment of AD patients, there was a significant difference between baseline and post-treatment scores on ACE and TMT. AD patients showed significant improvement in cognitive domains. Post-treatment reaction times on both parts of TMT were significantly reduced. Deficient cognitive performance can be seen in the context of pathological factors involved in AD onset for instance neurofibrillary tangles and neuritic plaques in cognition related brain areas (frontal, temporal, parietal lobes), lesions of cerebral cortex weakening interconnections between cortical and subcortical brain regions, tau pathology in neocortical neurons, accumulated positive reactive microglia in substantia nigra and accelerated choline acetyltransferase, alpha-synuclein positive deposition, oxidative stress, grey matter atrophy, reduced synaptic density in frontal and parietal lobes, demyelination of subcortical white matter and periventricular areas. Our findings of improved cognition and task switching abilities in AD patients post-Huperzine-A treatment are consistent with previous studies showing improved mental status post eight weeks of Huperzine-A treatment. Longer use of Huperzine-A, for instance twelve weeks can improve mood, behavioral problems, activities of daily living and cognition in AD patients. Huperzine-A is a reversible acetylcholinesterase inhibitor which has neuroprotective characteristics. Animal model studies demonstrated its counteracting effects on OP intoxication by reducing glutamate induced cell death.
ischemia, staurosporine and hydrogen per oxide. This mechanism reduces oxidative stress, protects mitochondria, interrupts metabolism of amyloid precursor protein, and regulates apopotic protein expression, nerve growth factor and its' related receptors. This study has a few limitations. Concerning the slow progressive nature of AD, six months may be a not long enough to observe the effects of Huperzine-A medication. It may also be difficult to differentiate from the placebo effects. Therefore, further investigation is needed to confirm this preliminary evidence. In conclusion, results of the current study have implications in every day clinical practice. Apart from other cognitive domains, task switching is an important ability to maintain daily life functioning. The study highlights that Huperzine-A is an effective therapeutic treatment to improve such dynamic human abilities in patients with AD.

ACKNOWLEDGMENTS

We thank hospital staff of Bahawal Victoria, Civil and Nishter hospital, Pakistan and participants of the study for their assistance in data collection.

REFERENCES