

## **EFFECT OF *CENTELLA ASIATICA* ON MILD COGNITIVE IMPAIRMENT (MCI) AND OTHER COMMON AGE-RELATED CLINICAL PROBLEMS**

Sushma Tiwari, Shinjini Singh<sup>a</sup>, Kishor Patwardhan, Sangeeta Gehlot, I.S.Gambhir<sup>a\*</sup>  
*Department of Kriya Sharir, Faculty of Ayurveda, Institute of Medical sciences, Banaras Hindu University, Varanasi, India*  
<sup>a</sup>*Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, India*

*Centella asiatica* is an herb used since ancient time in Ayurveda to improve mild cognitive functioning. The current study aimed to managing the cognitive functioning in elderly with mild cognitive impairment (MCI) and other age related problems. MCI is a serious problem which may be converted into Alzheimer disease. Although the concept of MCI is based on the presence of specific cognitive deficits, several study shows that these subjects can be develop depression, disruptive behavior (e.g agitation, aggression). The present study has conducted in sixty elderly subjects with written consent, registered at the geriatric out patient clinic at S.S. Hospital, BHU with age group 65 and above. The Diagnostic tools used in this study were Mini Mental State Examination, Activities of Daily Living, Instrumental Activities of Daily living and Yesavage Geriatric Depression scale. The *Centella asiatica* extract was prescribed in dosage of 500mg twice a day (1000 mg daily) for 6 months. An favorable improvement is observed in depression and other age related conditions like Hypertension, insomnia, loss of appetite, constipation etc.

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### **1. Introduction**

In recent years, the term 'Mild Cognitive Impairment' (MCI) is commonly being used to refer a stage of cognitive impairment prior to attaining clinical dementia in Alzheimer disease (AD) and related disorders[1]. The recent formulation of MCI follows previous attempts to characterize cognitive decline associated with aging, including benign senescent forgetfulness, age-associated memory impairment and age-associated cognitive decline [2, 3]. Therefore, this new concept is perhaps best considered as a stage in the difficult process of understanding and characterizing mild defects in cognition that do not fit clearly within the scope of established neurological and psychiatric disorders. This does not mean that someone with MCI will inevitably get Alzheimer's in their lifetime, but their likelihood of doing so is substantially increased [4]. MCI has now been categorized into two sub-types: those with the amnesic subtype (MCI-A) have memory impairments only, while those with the multiple cognitive domain subtype (MCI-MCD) have other types of mild impairments, such as in judgment or language, and mild or no memory loss. Both subtypes progress to Alzheimer's disease at the same rate, but they do have different pathologies in the brain [5]. MCI has been suggested as a term for a boundary area between normal aging and dementia, especially Alzheimer's disease. The search for an ideal drug or other

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\*Corresponding author: i\_gambhir@rediffmail.com

treatment modality to manage this condition is essential because it may be helpful to prevent the MCI patients for advancing into Alzheimer's disease.

*Centella asiatica* is a small creeping herb with shovel shaped leaves emerging alternately in clusters at stem nodes found in the Himalayan range. Extract of plant contains asiaticoside, in which a trisaccharide moiety is linked to the aglycone asiatic acid. In 'Ayurveda', this herb is used to promote healthy long life, improve memory and other cognitive domains. The other probable clinical uses of this plant are in venous insufficiency, wound healing, anxiety, anti-tumor, hypertension and peptic ulcer [6-13].

This study was an attempt to validate the effect of *Centella asiatica* extract in the management of mild cognitive impairment and other age-related problems among elderly patients.

## **2. Materials and methods**

This study was conducted in the geriatric clinic of Department of Medicine at Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, during the period of December 2006 to February 2008 (15 months), in accordance with the declaration of Helsinki guidelines on good clinical practice. This study was approved by Authors institutional ethical review board. A total of sixty subjects matched with our inclusion criteria, enrolled in the study with written consent from each patient.

All the subjects were aged 65 yrs and above, were screened for MCI using Mini Mental State Examination (MMSE) adjusted to educational status and age of the patient as the diagnostic tool [14]. The number of patients diagnosed to have MCI was sixty. These patients were prescribed powered *Centella asiatica* extract in the form of capsules in a dose of 500 mg twice a day for 6 months. A control group could not be had in the present study because of low prevalence of MCI.

For the preparation of drug dried leaves were obtained from the pharmacy of the faculty of Ayurveda, Banaras Hindu University, Varanasi. Cleaned leaves of *Centella asiatica* were dried in the shade (no direct exposure to the sunlight) and powdered by grinding. The appearance of the powder was brownish black. The powder was filled in capsules to distribute in the patients.

### **2.1 Inclusion criteria**

Patients aged 65 years and above with MCI, diagnosed on the basis of MMSE scores adjusted to educational status and age of the patient were included in this group.

### **2.2 Exclusion criteria**

Dementia according to DSM IV criteria, history of significant hearing or visual impairment, unable to participate in an interview in a meaningful manner, history of neurological disorders (stroke, Parkinson's disease, active epilepsy) or psychiatric illnesses (schizophrenia, mental retardation, depression and mania), other secondary causes of dementia including endocrine abnormalities and vitamin deficiencies. Individuals who were living alone were also excluded because the history and complaints could not be corroborated with another person.

### **2.3 Assessment criteria**

**1. History and clinical examination:** A detailed history was taken and physical examination performed.

**2. MMSE:** The mini-mental state examination (MMSE) was used as a screening test for cognitive impairment which is developed by the Indo-US Cross-National Dementia Epidemiology Study.

**3. Interview from care-giver:** Information about elderly social or occupational functioning, daily activity, and any risk factor- were obtained from caregiver according to Proforma prepared.

4. **Activities of daily living:** Information regarding normal routine work of elderly people was assessed by this scale. This is highly informative and closely related to mild cognitive impairment. This is adapted from Katz scale [15].

5. **Instrumental activities of daily living:** For this Lawton Instrumental Activities of Daily living (IADL) has been useful in rehabilitation settings to monitor improvements over time. IADLs are those activities whose accomplishment is necessary for continued independent residence in the community. The instrumental activities of daily living are more sensitive for subtle functional deficiency than the ADLs.

6. **Yesavage Geriatric Depression scale:** Yesavage Geriatric Depression Scale (short – version) was used to screen the subjects for depression. It contains 15 questions and each “depressed” answer is awarded one score. According to its norms, the scoring above 5 indicates depression. While  $7 \pm 2$  scores indicate mild depression and scoring  $11 \pm 2$  indicates severe depression [7].

7. **Hematological investigations:** Apart from the physical, physiological and psychological assessments, certain hematological investigation likes hemoglobin, Erythrocyte sedimentation rate, total serum protein, Total Leukocyte Count , DLC, CBC, PT were also conducted.

8. **Liver function tests:** SGPT and SGOT were conducted in the hospital laboratory.

9. **ECG:** ECG was done in a few patients depending on the need.

#### 2.4 Statistical analysis

The data analysis was done by using Statistical Package for Social Sciences (SPSS) Software Version 11.5.  $\chi^2$  and paired t test was done. All the results were considered statistically significant at p value  $\leq 0.05$ .

### 3. Results

MMSE scoring was done in sixty patients. A control group could not be had in the present study because of low prevalence of MCI. Family ignorance, economical problems and unawareness towards the disease are other common problems making a low patient input in the clinic. Also, retirement from the employment at this age leading to clinical depression is probably the other cause of reluctance of patients in seeking medical help.

A statistically highly significant ( $t = 9.68$   $p < 0.01$ ) improvement in mean MMSE scores was observed after treatment with the drug (Table 1).

Table 1: Effect of *Centella asiatica* on Mini- Mental State Examination

	Mean $\pm$ S.D.		Intra group comparison paired t-test
	Before Treatment	After Treatment	
M.M.S.E.	25.05 $\pm$ 1.19	28.35 $\pm$ 1.39	t = 9.68 p<0.01

A statistically highly significant decrease in mean Diastolic BP (before treatment= 85.70  $\pm$  18.56, after treatment= 78.50  $\pm$  10.82) was observed after treatment with the drug ( $t = 2.22$   $p < 0.05$ ). The drug had a statistically significant effect of improving the appetite among the patients ( $\chi^2 = 17.50$ ,  $p < 0.001$ ). A significant improvement in the sense of well-being was observed in most of the patients after treatment ( $\chi^2 = 32.48$   $p < 0.001$ ) (Table 2).

Table 2: Effect of *Centella asiatica* on sense of well being.

Sense of well-being	Before Treatment		After Treatment	
	No. of cases	%	No. of cases	%
Absent	57	95	0	0
Present	3	5	60	100
Total	60	100	60	100

Before treatment, the total number of individuals complaining of loss of sleep was 54 (90%), after treatment the number reduced to 3 (5%). ( $\chi^2 = 25.66$   $p < 0.001$ ) (Table 3).

Table 3: Effect of *Centella asiatica* on Insomnia

Insomnia	Before Treatment		After treatment	
	No. of cases	%	No. of cases	%
Absent	6	10	57	95
Present	54	90	3	5
Total	60	100	60	100

Table 4 Distribution of cases as per type of MCI.

Table 4. Distribution of cases as per type of MCI

Type of MCI	No. of cases	Percentage
Amnesic	54	90
Multiple cognitive domain	6	10
Total	60	100

Table 5 Normative Data on the MMSE, as per Crum et al. (13)

Table 5. Normative Data on the MMSE, as per Crum et al. 1993.

Education	Age													
	18-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>84
4th grade	22	25	25	23	23	23	23	22	23	22	22	21	20	19
8th grade	27	27	26	26	27	26	27	26	26	26	25	25	25	23
10 <sup>th</sup>	29	29	29	28	28	28	28	28	28	28	27	27	25	26
College	29	29	29	29	29	29	29	29	29	29	28	28	27	27

#### 4. Discussion

In the present study, the MMSE scoring showed significant improvement after administration of *Centella asiatica* for 6 months in elderly with Mild Cognitive Impairment. This finding indicates that *Centella asiatica* is useful clinically in the patients suffering from MCI. The mode of action of *Centella asiatica* in this condition is probably due to its cholinergic activity, anti oxidant activity or anti inflammatory activity. A few studies have already shown that *Centella asiatica* has cholinomimetic, anti inflammatory and antioxidant properties. In the study of Somchit et al, the water extract of the herb revealed significant antinociceptive activity which was statistically similar to aspirin. The extract also revealed significant anti-inflammatory activity which was statistically similar to the non-steroidal anti-inflammatory drug, mefenamic acid [11]. In the study of Sakina et al, the *Centella asiatica* extract has been shown to have potentially cholinomimetic activities in vivo [12]. Another significant effect of *Centella asiatica* is that it acts as an anti oxidant [13]. *Centella asiatica* also accelerates nerve regeneration upon oral administration and contains multiple active fractions increasing neurite elongation in vitro [16].

The present study shows that maximum patients with MCI were in the age group of 65-69 years. In the present study, maximum number of patient with MCI had education of collegiate level. This finding is also not consistent with other studies [17, 18]. But, with a small sample size, no conclusive remarks can be drawn on this aspect.

There was no statistically significant change observed in mean SGOT and SGPT levels after treatment with *Centella asiatica*. Jorge et al had reported the hepatotoxicity due to *Centella asiatica* in few patients [19]. The present study is not suggestive of any hepatotoxicity and therefore, the drug may be generally considered safe enough to be administered among elderly.

In the present study, before treatment, the total number of individuals complaining of numbness and burning was 45 (75) % and after treatment, the number reduced to 15 (25%) ( $\chi^2 = 8.10$ ,  $p < 0.01$ ). This observation is suggestive of a possible role of *Centella asiatica* in the management of peripheral neuritis. The mode of action requires to be investigated. Sun et al had already reported that *Centella asiatica* is effective in numbness and burning [16].

A significant improvement in the sense of well-being was observed in most of the patients after treatment with *Centella asiatica* ( $\chi^2 = 32.48$   $p < 0.001$ ). This may be probably due to anxiolytic and tranquilizing effects of the drug, which have been proposed by some other workers as well [21]. Present study shows that the total number of individuals complaining loss of sleep (either problem in initiation of sleep or in maintenance of sleep) before treatment was 54 (90%) and after treatment the number reduced to 3 (5%) ( $\chi^2 = 25.66$   $p < 0.001$ ). This shows that the drug has a potential tranquilizing effect which has been proposed by some earlier studies also [21].

Total number of individuals complaining loss of appetite was 45 (75 %) before treatment; and after treatment the number reduced to 15 (25%) ( $\chi^2 = 25.66$   $p < 0.001$ ). This effect needs to be further investigated.

A statistically highly significant decrease in mean Diastolic Blood Pressure was observed after treatment with the drug. The effects of *Centella asiatica* on cardiovascular system have not been investigated so far and this finding may be of value in treating the hypertensive individuals with MCI. The probability is that the drug may be causing a fall in peripheral resistance by producing vaso-dilatation through some un-known mechanism.

#### 5. Conclusion

The aim of present study was to assess the role of *Centella asiatica* in the management of Mild Cognitive Impairment (MCI) among elderly, aged 65 years and above and also to assess its utility in other age-related clinical problems. The mean MMSE scoring showed significant improvement after administration of *Centella asiatica* for 6 months in elderly with MCI. This finding indicates that *Centella asiatica* is useful clinically in the patients suffering from MCI. This drug is also having favorable effects in diastolic blood pressure, peripheral neuritis, insomnia, loss of appetite etc. In a nutshell, the present study is indicative of multiple useful clinical effects of

*Centella asiatica* especially in the age-related cognitive decline. However, the mechanism of action and possible toxicity needs to be further investigated in a large sample. Also, a double blind randomized clinical trial is essential.

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