World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.088

BRAHMI GHRITA: A POTENTIAL DRUG FOR TREATMENT OF MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE

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Article Received on 04/06/2018 **Article Revised on 25/06/2018** **Article Accepted on 16/07/2018**

ABSTRACT

In the anticipation of disease modifying treatments for Alzheimer's disease, Brahmi Ghrita, a polyherbal Ayurvedic medicine traditionally used for enhancing memory and cognition, was tested on 30 diagnosed patients of mild cognitive impairment (MCI) due to Alzheimer's disease. Donepezil, a contemporary treatment, often results in vivid side-effects. The study was conducted to compare the effect of Brahmi Ghrita and Donepezil in MCI due to Alzheimer's Disease.

KEYWORDS: Alzheimer's Disease, MCI, Brahmi Ghrita, Ayurveda.

INTRODUCTION

Alzheimer's Disease is a progressive form of dementia. Although a lot of research work is going all over the world, the exact diagnosis as well as efforts to find a cure for AD have been disappointing, and the drugs currently available to treat the disease have limited effectiveness and address only its symptoms. The underlying pathogenesis is loss of neurons in the hippocampus, cortex, and subcortical structures. Substantial evidence suggests that inflammation has a causal role in Alzheimer's Disease pathogenesis.[1,2] and understanding and control of interactions between the immune system and nervous system might be key to prevention or delay of disease. The early symptoms may include short-term memory loss, difficulty or inability in learning new information, mood swings, words finding difficulty, forgetting names, and losing items. The emotional features commonly include frustration, aggression, and irritability. In severe cases, complete loss of memory, disappearance of sense of time and place and complete incontinence are the presenting features. Patients become totally dependent upon the caregivers and eventually require round-o-clock care. Thus, AD presents a considerable problem in patient management. It is believed that therapeutic intervention that could postpone the onset or progression of AD would be the treatment of choice.

Mild cognitive impairment (MCI) is considered as prodromal stage of an impending dementia, particularly AD. Memory problems which do not meet the diagnostic criteria of dementia is known as MCI. There is no proper cut-off point to separate MCI from dementia. But this is the stage to decide the management protocols of present and forthcoming consequences. Several herbal medicines opt to modify the progress and symptoms of AD. Ayurveda is an Indian system of traditional medicine, which have developed a number of medicinal preparations that are carefully standardized, and their efficacy and safety for a specific application have been demonstrated. This modernization of traditional system appears to be meeting a thrust in health-relevant areas.[3]

A considerable part of Ayurvedic literature deals with the nervous system and disorders associated with it. The health of a person depends on balance of three vital energies in the body i.e. Vata (Air humor), Pitta (Biological fire humor) and Kapha. Nervous system disorders are mainly due to imbalance in Vata and partial involvement of Pitta and Kapha. Vata is responsible for movement of impulses through the brain and the nerves which control both voluntary and involuntary functions. Vata derangements always results in some weakness, disturbance, or hypersensitivity of the nervous system resulting in, problematic conduction, dryness and death of neurons. Likewise, Pitta which is responsible for digestion and assimilation plays a vital role in either accumulation or clearing out of neuro fibrillary tangles and tau proteins. Kapha which provides nourishment and sliminess to the synapses helps in proper conduction which is also compromised in the pathogenesis. This science explains several herbs for nervous system

disorders, including memory loss specifically in older adults, but the recent advancement in studies on the role of these medicines in nervous system disorders and dementias, including dementia associated with AD is remarkable.[4,5]

Our aim was to investigate the cognitive response of prescribed polyherbal Ayurvedic Drug Brahmi Ghrita[6] on Mild Cognitive Impairment due to AD. We conducted the trial on 30 diagnosed patients of MCI due to AD. The cases were compared with patients undergoing allopathic treatment of MCI (Donepezil 10mg/day and the data was evaluated with respect to score changes in ADAS- Cog scale. The serum samples were collected for studying the effect of drug on inflammatory markers also.

MATERIALS AND METHODS

It was an open label, single centered, comparative, prospective, pragmatic trial. The trial protocol and related documents were reviewed and approved by the Institutional Ethical Committee, Institute of Medical Sciences, Banaras Hindu University, Varanasi, U.P., India. The study was conducted in accordance with Indian Council of Medical Research (ICMR) ethical guidelines for biomedical research on human participants. Trial had registered in the clinical trial registry of India (CTRI/2017/07/009171).

Primary and secondary outcome measures

Primary outcome measure of study was to evaluate efficacy of Ayurvedic formulation Brahmi Ghrita in the subjects suffering from Mild cognitive impairment due to Alzheimer's Disease by assessing change in ADAS- cog scale and 3MS (Modified Mini Mental Examination Score) total Score. The secondary outcome measures was to compare the effect of Brahmi Ghrita with well-established trial drug Donepezil.

Trial interventions – Brahmi Ghrita at a dose of 12 gm was given twice a day empty stomach (Pranodana Kala) with luke warm water as Anupana for 90 days. The trial drug was acquired from the Ayurvedic Pharmacopoeia of India complied GMP (Good manufacturing practice) certified company.

Bramhi Ghrit (As. Hr. Ut. 6/23- 23)

- Brahmi Swaras- *Bacopa monnieri* Fam. Sorophulariaceae
- Goghrit - clarified butter
- Shunthi – *Zingiber officinale Roscoe* Fam. Zingiberaceae
- Maricha – *Piper nigrum Linn.* Fam. Piperaceae
- Pippali – *Piper longum Linn.* Fam. Piperaceae
- Shyama Trivrit- *Operculina turpethum* Fam. Convolvulaceae
- Danti- *Boliospermum montenum Muell- Arg* Fam. Euphorbiaceae
- Shankhapushpi- *Convolvulus pluricaulis, Chois.* Fam. Convolvulaceae
- Chhitvan Twak – *Alstonia scholaris R. Br.* Fam. Apocynaceae
- Vidang – *Embelia ribes Burm.* Fam. Myrsinaceae.

Inclusion criteria

Subjects of either sex, age between 40 years and above, fulfilling the criteria of MCI due to AD (Cognitive performance of at least 1 SD below the age and education norm in one or more of the following domains: verbal learning and memory, non-verbal learning and memory, verbal fluency, naming, visuoconstruction, information processing speed, executive functions, as demonstrated by the appropriate neuropsychological tests), Decline in cognitive function from a previously higher level of ability, without any other probable and possible cause of dementia and willing to participate in the study for 90 days were included in the study.

Exclusion criteria

Patients with dementia, any kind of kidney disorders, early onset of a focal seizure, previous or ongoing depression, early prominent gait disturbance with only mild memory loss, resting tremor with stooped posture, the early appearance of Parkinsonian features in association with fluctuating alertness, visual hallucinations, or delusional misidentification suggests, chronic alcoholism, vitamin B12 deficiency, chronic drug intoxication and dementia with any other explainable cause. Further, patients with gross disability in performing daily normal routine, past history of atrial fibrillation, acute coronary syndrome, myocardial infarction, stroke or severe arrhythmia in the last 6 months, severe renal or hepatic disorders, Pregnant and lactating woman were also excluded from the study.

Withdrawal criteria

The subjects were free to withdraw themselves from the trial at any time without the authorization of researcher or any reason.

Study procedures

Informed written consent was taken from the patient on the first visit. General, systemic and biochemical examinations were done. Total 60 subjects who fulfilled the inclusion and exclusion criteria were enrolled for the trial. The patients who were on any kind of anti inflammatory treatment or anticholinergic treatment were kept on a 28 days washout period before enrollment. The screening of enrolled subjects was done by ADSA –cog and 3MS.The enrolled subjects were randomly divided into two groups. Group I – were treated with Donepezil 10 mg/day for next 90days. Group II – was treated with Brahmi Ghrita 12 gm empty stomach BD (Pranodan Kala) with Luke warm water for 90 days.

Follow-up assessment

Subjects were visited for follow-up visits on day 30 (Visit 1), day 60 (Visit 2), day 90 (Visit 3). On each follow-up visit, patient's general and systemic physical examinations were done. Assessment of the cognitive and other symptoms of MCI were done on ADAS –cog and 3MS. Blood serum samples were collected on Day 1

and Day 90 for recording the change in level of inflammatory markers.

Statistical analysis- The analysis of the data using statistical software SPSS 15.0 data describing quantitative measures are expressed as median or mean ± SD or SE or the mean with range.

All p (probability) values are reported based on two-sided significance test and all the statistical tests are interpreted as significance at 5% level ($p < 0.05$)

Sample Preparation and Data Acquisition

Table-1.

Sample characteristics		Donepezil (*N* = 30)	Brahmi Ghrita(*N* = 30)
Female: Male		12:18	14:16
Education		19.05 ± 4.40	18.47± 4.44
Age		46.4 ± 8.4	43.66 ± 3.24
ADAS -Cog	**BT**	22.05 ± 3.91	21.56 ± 4.05
	AT	20.91 ± 4.41***	20.16 ± 4.64**
3 MS	**BT**	77.41 ± 4.50	69.63 ± 5.02
	AT	78.91 ± 4.59**	79.88 ± 4.15**

***p<0.05, **p<0.01, ***p<0.001**

Mean ± standard deviation. Modified Mini-Mental-State Examination (3MS) normal range: 1-100. Alzheimer's disease Assessment scale (ADAS-cog) normal range: 0–70.

In the primary intervention the statistical analysis shows that Brahmi Ghrita is significantly capable of prolonging the progression of cognitive impairment. For 3MS scores the p value <0.01 and for ADAS- Cog also the p value <0.01 which denotes that Brahmi Ghrita may be a potential drug to treat MCI due to Alzheimer's Disease.
In the secondary intervention, while comparing the effect of Brahmi Ghrita with the group treated with donepezil, here we can see that both the groups shows significant results in ADAS- Cog test as well as 3MS (Modified Mini Mental State Examination).

Frequency of Adverse events according to study group

Table-2.

Characters	Donepezil n=30	Brahmi Ghrita n=30
Diarrhea	20%	0%
Vomiting/ nausea	16.6%	3.33%
Insomnia	3.33%	0%
Leg cramp	3.33%	0%

Some side effects have been noted in the donepezil treatment group. 20% (6/30) have encountered diarrhea, 16.6% (5/30) have encountered nausea and vomiting, 3.33% (1/30) has encountered leg cramp and insomnia. There were no any remarkable side effects noted in Brahmi Ghrita treatment group in this trial period of 3 months.

DISCUSSION AND RESULT

This study was conducted on patients having mild cognitive impairment due to Alzheimer's disease. The patients had memory problems, which distinguish them from normal aging adults but were not categorized under dementia and did not display significant depressive symptoms. Functional impairments characteristic of early AD were almost absent.

There is "Selective alteration" in neurons of the brain termed as sites of "Khavaigunya" (physiologically frail segments). This alteration is produced due to deviated metabolism created by the malfunctioning of Agni (Agnivaishamya). Because Agni is responsible for each and every catabolic and anabolic activity, this leads to down regulation of cholinergic receptors like acetyl choline esterase and CHAT that are prodromal cause of cognitive impairment and by accumulation of neuro fibrillary tangles and increase the pathology of the disease. In a nut shell we see that there is Agnimandhya leading to metabolic disorganization in brain which results in Aam (NFTs, Tau etc) accumulation. This Aam causes neurodegeneration and ultimately death of neurons. Brahmi Ghrita is a combination of drugs having multi domain activity like Agni Vardhan, Aam Pachan, Aam Shodhan and neuroprotection which are the desirable treatment for Mild cognitive impairment due to Alzheimer's Disease.

The findings from this study have suggestions for the design of future efficacy trials for MCI as they provide outcome measures with minimal side effects. In designing this study, investigators expected that there would be a decline in cognitive function of the Brahmi Ghrita group over the 12-week treatment period (as seen in patients with mild to moderate AD and predicted if MCI is prodromal AD). The lack of decline in Brahmi Ghrita treated subjects over 3 months indicates that loss of cognitive function occured more slowly with respect to the subjects of MCI due to AD. Thus, efficacy trials may require trials of longer duration to adequately test for symptomatic treatment effects and research on the pharmacokinetics of the new trial Drug "Brahmi Ghrita." Finally, the finding that patients with MCI show

improvement on some cognitive tests may have implications for developing other traditional medicinal plants-based treatment strategies for patients with MCI due to AD.

Research intervention

Although donepezil shows significant improvement in condition of Mild cognitive impairment due to Alzheimer's disease but it is accompanied with a lot of side effects. Brahmi Ghrita on the other hand showed improvement in diseased as well as was not associated with any remarkable side effect. But the research conducted was of short duration (3 months), further research is needed on pharmacokinetics of Brahmi Ghrita.

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