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Efficacy of *Brahmighruta* in Mild Neurocognitive Disorder - A Randomized Controlled Trial

Research Article

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Abstract

Context: Mild Neurocognitive Disorder (NCD) due to possible Alzheimer's disease (AD) is the most common cause and lacks adequate management strategies. Aims: Current study aims to evaluate the efficacy of *Brahmighruta* (Ayurveda Medicine) on Mild Neurocognitive Disorder due to possible Alzheimer's disease. Settings and Design: Study was a randomized controlled parallel group trial. Methods and Material: Total 52 patients meeting the DSM V criteria of mild NCD due to possible AD, above 60 years of age, either sex participated in the study. They were randomly divided into two groups, Group I received donepezil 10 mg once a day for 90 days and group II received *Brahmighruta* 10ml twice a day before food with warm water for 90 days. Assessments were through Mini mental state examination (MMSE), Alzheimer's disease Assessment Scale-Cognitive subscale (ADAS-Cog), Disability Assessment for Dementia (DAD), Cornell Scale for Depression in Dementia (CSDD), DEMQOL (version 4) and UKU Side effect scale. Assessments were on every 15th day. Results: Effect of *Brahmighruta* and donepezil were comparable in MMSE (p=0.67), ADAS Cog (p=0.16), DAD (p=0.07), CSDD (p=0.29), DEMQol (p=0.14). Effect size was large. Improvements were observed in both the groups on within group assessments. Eight mild adverse events were noted with Donapezil but non with *Brahmighruta*. Conclusions: Brahmighruta and Donapezil showed similar improvements in all outcome measures. Due to lack of adverse effects Brahmighruta may be a preferred substitute for Donapezil. Needs further studies.

Keywords: Mild Neurocognitive disorder, Alzheimer's disease, *Brahmighruta,* Donapezil.

Introduction

Neurocognitive disorders (NCD) are a primarily an acquired cognitive disorder. It has mild and major categories. Mild NCD was first introduced in DSM IV (1) under the section "Cognitive Disorder Not Otherwise Specified." It has undergone extensive revision in DSM V. (2) DSM V suggests 10 etiological causes for mild and major NCD. Major difference in mild and major NCD is that mild NCD have modest cognitive decline and can function independently but it is lost in major NCD. (3) Other descriptors of NCD are possible or probable category, associated with behavioural disturbances and severity of disability.

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Mild cognitive impairment (MCI) is similar to Mild NCD but is dependent on age and aetiology. It varies from 3 to 22%. (4) Incidence is 1-6% per year. (5) NCD differs from dementia mainly in the age criteria. Dementia is the degenerative disorder in elderly, however NCD is the expanded criteria with inclusion of any age. Across the globe, 50 million suffer from dementia and is projected to raise to 152 million by 2050. About 66% of sufferers are from low-income and middle-income countries. World wide cost of dementia is around US$1 trillion annually. (6) Progression rate is 10%-15% per year in persons with amnestic form of mild cognitive impairment to clinically diagnosable Alzheimer's disease, however in normal elderly persons it is 1-2%. (7) The number of patients with dementia almost doubling every 20 years. (8) Prevalence of cognitive impairment in people of above 65 years, from north to southern parts in India ranges from 3.5% to 11.5%. (9)

Cognitive impairment is in one or more domains like memory (amnestic MCI), attention, language, visuospatial skills, perceptual speed or executive functioning. Multidomain MCI is considered in either

amnestic or non-amnestic domains involvement. Alzheimer's disease is the leading cause of dementia and possibly even to NCD. Diagnosis of NCD is through subjective complaint of cognitive decline along with confirmation by standard neuropsychological testing. This will help in assessing decline in various cognitive domains like learning and memory, language, executive functions, visuospatial function. Biomarkers are amyloid-β (Aβ), tau-mediated neuron injury, and neuronal loss. Neuro imaging studies suggest neuronal atrophy in the regions pertaining to NCD (10) and amyloid deposition in brain. Functional neuroimaging suggests glucose hypometabolism in areas of AD.

Alzheimer's disease (AD) is a multifactorial progressive disease. More than 200 drug trials have failed in the last decade and no new drug is approved by FDA since 2003. (11) Reasons for this could be late initiation of treatment during the disease course, inadequate knowledge of complex pathophysiology of AD. AD appears not to be a single disease but of different subtypes. (12) It has multiple potential contributors like trauma, inflammation, insulin resistance, vascular compromise toxins, infections and trophic withdrawal. AD is unique to each individual, and has different in genetics, epigenetics, biochemistry, subtypes and hence different response to treatments. (13) Superior outcomes are reported when multiple contributors are taken into account and addressed through personalized multitherapeutic approach. However best outcome from clinical trials have been to delay progression of cognitive decline than arresting decline.(11) Life style components like physical activity, mental challenges, energy restriction, socialization and Mediterranean diet have preventive role in AD. (14) Most widely studied intervention on MCI is cholinesterase inhibitors and are unpromising. Systematic reviews of randomised controlled trials of all cholinesterase inhibitors, donepezil and galantamine showed a marginal benefits which are outweighed by adverse events risks, and unexplained raised mortality rate with glantamine. (15) Management of AD includes inhibitors to cholinesterase and antagonists to *N*-methyl d-aspartate. Donepezil has shown trivial benefits in cognitive function, activities of daily living and clinician-rated global clinical state in AD. (16) Physical activity, cognitive training, (17) and mediterranean diet (18) can reduce the disease progression. Among alternative and complimentary medicine, Chinese medicine has shown to produce beneficial effect in cognitive decline . (19) *Brahmighruta* is an Ayurveda formulation with a therapeutic effect in geriatric care and nootropic effect. Major ingredient is *Brahmi* (*Bacoppa monnieri*) has demonstrated nootropic effect. (20,21) Current study was planned to evaluate the effect of *Brahmighruta* in mild NCD due to possible AD.

Subjects and Methods

Enrolment of the patients was from the outpatient department of the institute. CONSORT statement guidelines (22) were used to report the study.

Subjects

Fifty two patients diagnosed as Mild Neurocognitive disorder due to possible sub type of Alzheimer's disease as per DSM V criteria (2) were enrolled.

Inclusion criteria

Age above 60 years of either sex, diagnosed as Mild Neurocognitive Disorder criteria due to possible sub type of Alzheimer's disease and Mini Mental State Examination (MMSE) < 24.

Exclusion criteria

Patients with other Neurocognitive disorders like Parkinson's disease, substantial neuropsychiatric or behavioural symptoms, with severe or uncontrolled somatic disorders, with clinically relevant depression (Cornell Scale for Depression in Dementia (CSDD)>10), on any other medications like psychotropic, neurotropic etc since 4 weeks, with substance abuse like alcohol, tobacco etc. were excluded from the study.

Screening methods

All the patients were thoroughly assessed clinically and medical history was reviewed. Relevant laboratory assessments were carried out to screen the underlying medical conditions.

Each patient underwent a thorough clinical evaluation, and their medical records were examined. The possible underlying medical issues were screened through appropriate laboratory assessments. *Ayurveda* assessments like *prakruti* were also carried out and data was recorded.

Research design

Study was a randomized, controlled, parallel group comparative clinical study. Randomization, distribution, and administration of study materials were handled by a separate staff, independent from the investigators. Random sequence generation was produced using the online programme "Random Number Generator". Sequence generation and sealing them was carried out by Principal investigator. Allocation was concealed through sealed opaque envelopes. After patient enrolment, independent assistant not involved in the study opened the envelopes sequentially. Block size was 2. The patients were allocated in control and intervention groups in 1:1 ratio. Adherence was assessed through the unused medicine and the adherence chart. Based on a previous publication (23), MMSE, one of the primary outcome criteria of the current study was used sample size calculation. Estimated effect size of d=0.89, 5% alpha error (two tailed as direction was not hypothesised), 90% power, we estimated that we require 26 participants in each group.

Intervention

All the patients (n=52) were randomly divided into two interventional groups: group I and group II. Group I (n =26) received tablet donepezil 10 mg once a

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day after food with water for 90 days. Group II (n = 26) received *Brahmighruta* 10ml twice a day before food with warm water for 90 days. Donepezil is used in mild cognitive impairment in Alzheimer disease. (24)

Brahmighruta (25) is a formulation explained in classical text books of Ayurveda. Preparation of *Bramhi ghruta* was carried out at GMP (Good manufacturing practice) certified KLE Ayurveda Pharmacy, Khasbhag, Belagavi Karnataka India. The *Brahmighruta 's* ingredients were procured from the reliable distributors. The Central Research Facility, an AYUSH-approved ASU drug testing facility in Belagavi, Karnataka, India, performed raw material authentication. API (Ayurvedic Pharmacopeia of India) guidelines were used for raw material and finished product qualitative analysis. Raw drugs assessments were ash values, extractive values and loss on drying. Finished product, *Brahmighruta* macroscopic assessments were form, colour, taste, physicochemical standards like loss on drying, refractive index, saponification value, Iodine value and acid value were carried out. Donepezil was procured from Ryon Pharma pvt. ltd (Ludhiana ,India) batch no-3664 (Mfg.Lic.No-1889-0SP). Total duration was for 90 days with follow up assessment on every 15th day. Patient information sheet was provided after explaining the study and informed consent was obtained. Study was conducted in accordance with the declaration of Helsinki. The study was approved by the Institutional Ethics Committee (Protocol Id BMK/18/ PG/KC/05, KAHER's BMK Ayurveda Mahavidyalaya Belagavi, Date of Approval 3/06/2019 and CTRI Registration Number CTRI/2019/08/020596). Data collection was from January 2020 to May 2021. Patients experiencing any distressing manifestation were asked to report and screened for the possible adverse events.

Criteria for assessment

Primary outcome criteria

Mini mental state examination (MMSE) (26) evaluates 6 cognitive domains (27) namely visuospatial, language, concentration, working memory, memory recall and orientation. Total scores range from 0-30. Lower the scores suggests of greater cognitive impairment. Severity levels range from mild severity ≥20, mild to moderate 10–26; moderate to severe < 14; and severe < 10. (28)

Alzheimer's disease Assessment Scale-Cognitive subscale (ADAS-Cog).(29) ADAS Cog evaluated 3 cognitive domains (30) memory, language and praxis. Total scores range from 0-70. Greater the score, greater is the dysfunction. Scores higher than 18 suggests greater cognitive impairment. Four point change in 6 months intervention is considered to be clinically significant. (31)

Secondary outcome Criteria

Disability Assessment for Dementia (DAD) is a functional assessment measure (32), Cornell Scale for Depression in Dementia (CSDD) (33), DEMQOL (version 4) (34) scale measures quality of life and UKU Side effect scale. (35)

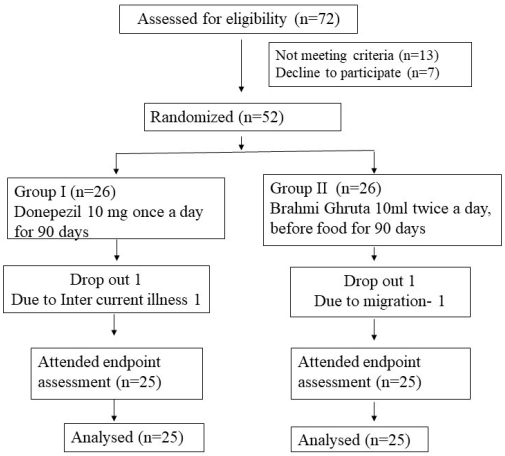
Statistical methods

Statistical analysis was carried out using SPSS Version 25.0 (IBM Corporation, Chicago, Illinois, United States). Homogeneity of data across groups was assessed through $\chi 2$ test. Two way repeated measure Analysis of Variance (rmANOVA) with Bonferroni post-hoc test was used to compare groups across different time points. Outcome of the interventions was through the difference of pre and post values. Within group comparison at two time points was analyzed by paired T test. Independent sample t test was used to compare groups at a time point. Effect size was calculated by Partial Eta Square method, effect of interventions through changes from pre to post interventions were used for analysis. Effect size was interpreted as minimal (0-0.2), small (0.2-0.5), medium (0.5-0.8) and large effect (above 0.8) (36). Values are reported as mean ± standard deviation. Statistically significance was set at $p < 0.05$.

Results

Fifty two participants were enrolled in the study. 25 participants in each group completed the study. One patient from each group dropped out. Reason was intercurrent illness in one patient and in other was migration. (Fig No.1)

Figure 1: CONSORT Chart



Patient profile-

Mean age of the patients was 69.07 years. Majority of patients were male (53.8%), middle socioeconomic status (73%), vegetarian diet pattern (76.9%), graduate (42.3%), *Vata prakurti* (40.3%), widow (42.3%). Mean duration of illness was 2.8 years. Mean BMI was 23.13 and mean weight was 56.86 kgs.

The mean age (p=0.22), gender (p=1), socio economic status (p=0.48), education (p=0.41), diet pattern (p=0.35) were comparable between groups (Table No 1). Clinical variables like *prakurti* (p=0.83), weight (p=0.07), body mass index (p=0.62) of the patients were comparable in both the groups. Duration of illness was more (p=0.02) in group II (Table No 1). Clinical assessments like Systolic blood pressure (SBP), Diastolic blood pressure (DBP), MMSE, ADAS Cog, DAD, CSDD, DEMQol were comparable between the groups. (Table No 2, Fig 2)

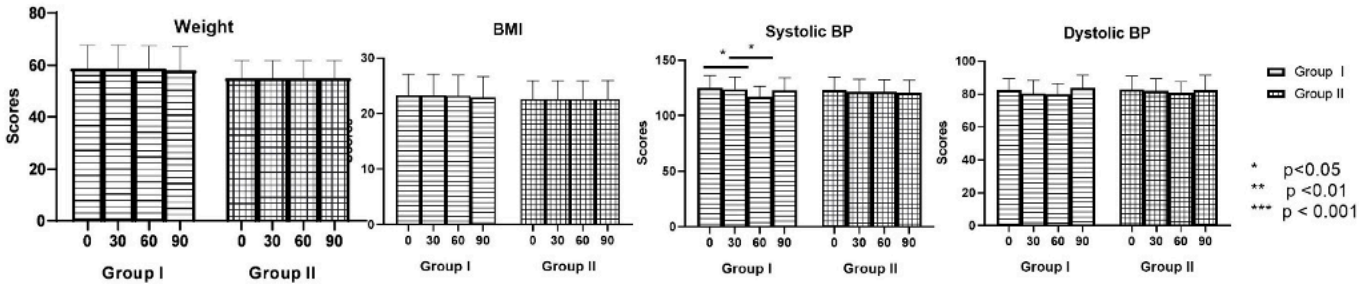
Table 1: Patient profile : Expressed in Mean, standard deviations (S.D.) and percentage.

Sl. No.	Clinical profile		Group I	Group II	No & %	p
			No	No		
1	Age (yrs)		67.96 ±6.74	70.19 ±6.34	69.07 ±6.57	0.22
2	Gender	Male	14	14	53.84%	1
		Female	12	12	46.15%	
3	Socioeconomic Status	Higher class	4	4	15.38%	0.48
		Middle class	19	19	73.07%	
		Lower class	3	3	11.53%	
4	Diet	Veg	20	20	76.92%	0.35
		Non veg	6	6	23.07%	
5	Education status	Primary	8	8	30.76%	0.41
		High school	7	7	26.92%	
		Graduate	11	11	42.30%	
6	Marital status	Married	13	13	50%	0.36
		Unmarried	2	2	7.69%	
		Widow	11	11	42.3%	
7	Prakruti	Vataja	11	10	21 (40.38%)	0.83
		Vata pitta	7	7	14(26.92%)	
		vata kapha	3	5	8 (15.38%)	
		Pitta kapha	2	1	3 (5.76%)	
8	Duration of illness (yrs)		2.53±0.81	3.07±0.89	2.80±0.88	0.02
9	Drop outs		1	1	3.84%	
10	Study completed		25	25	96.15%	
11	Total		26	26	52	

Table 2: Baseline characteristics in both the groups

S.no	Parameters	Group I	Group II	P
1	Weight (Kgs)	58.78±8.74	54.94±6.52	0.07
2	BMI (Kg/M2)	23.37±3.79	22.88±3.34	0.62
3	SBP (mm of Hg)	124.23±11.01	123.07±11.58	0.71
4	DBP (mm of Hg)	83.07±6.79	82.69±7.77	0.85
5	MMSE	16.92±1.19	16.26±0.92	0.07
6	ADASCog	31.15±3.58	32.34±4.07	0.26
7	DAD	73.04±7.54	74.74±3.73	0.30
8	CSDD	7.15±1.04	7.26±1.11	0.70
9	DEM Qol	64.76±4.01	63.69±3.23	0.29

Figure 2. Effect of Interventions on weight, BMI, Systolic and diastolic blood pressure



3.2. Primary Outcome-

Effect of interventions on MMSE were comparable (p=0.67). Both the groups showed significant improvement at 60th and 90th day (p<0.0001). Similarly in ADAS Cog, interventions were comparable (p=0.16). Within group assessment showed significant improvements in both the groups at 60th and 90th day (p<0.0001). Effect size was large in both MMSE (2.25) and ADAS cog (1.29) favouring group II. (Table No 3) (Fig No 3)

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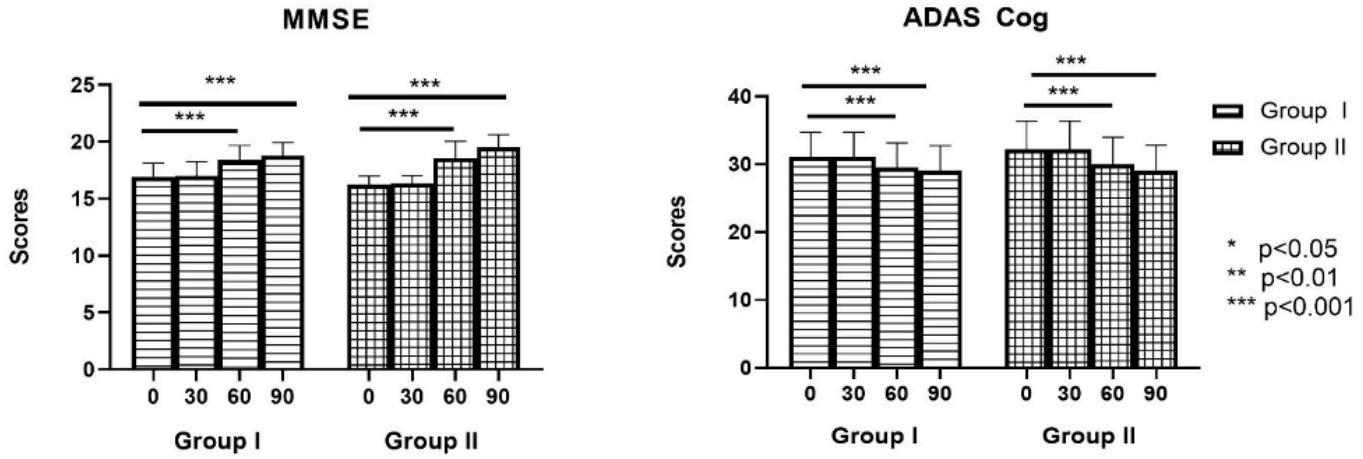
Table 3: Effect of intervention on various parameters. Expressed in mean and standard deviation

Sl.No	Group	Mean & Sd (O day)	Mean & Sd (30 day)	Mean & Sd (60 day)	90th day	P#-(0-30 days)	p#-(0-60 days)	p#-(0-90 days)	F value	P value	Effect Size (0-90 days)
1		Systolic Blood Pressure (mm of Hg)									
	I	125±11.03	123.75±10.95	117.08±9.54	122.91±11.22	1	0.03	1	0.05	0.82	0.05
	II	123.33±11.67	121.25±11.53	121.25±11.15	120.41±11.60	1	1	0.29			
2		Diastolic Blood Pressure (mm of Hg)									
	I	82.50±6.75	80.41±8.06	80±6.59	83.75±7.69	1	1	1	0.1	0.75	0.15
	II	82.91±8.06	82.08±7.21	80.83±6.53	82.5±8.96	1	1	1			
3		BMI (Kg/M2)									
	I	23.23±3.83	23.23±3.83	23.19±3.71	22.94±3.71		1	0.1	0.41	0.52	0.75
	II	22.60±3.31	22.60±3.32	22.61±3.31	22.63±3.32	1	0.97	0.29			
4		Weight (Kgs)									
	I	58.66±9.05	58.70±9.03	58.56±8.85	57.93±8.96	1	1	0.09	2.31	0.14	0.79
	II	54.98±6.80	55.01±6.82	55.02±6.80	55.05±6.81	0.53	0.35	0.27			
5		MMSE									
	I	16.91±1.21	17±1.25	18.37±1.31	18.79±1.14	0.97	<0.0001	<0.0001	0.18	0.67	2.25
	II	16.25±0.73	16.33±0.70	18.58±1.47	19.54±1.10	0.97	<0.0001	<0.0001			
6		ADASCog									
	I	31.04±3.68	31.04±3.68	29.54±3.61	29.04±3.70	-	<0.0001	<0.0001	2.06	0.16	1.29
	II	32.20±4.18	32.20±4.18	30±3.98	29.12±3.69	-	<0.0001	<0.0001			
7		DAD									
	I	72.63±7.67	72.63±7.67	75.22±9.42	79.14±7.43	-	0.005	<0.0001	3.57	0.07	0.96
	II	74.92±3.73	74.92±3.73	78.86±4.30	84.20±4.33	-	<0.0001	<0.0001			
8		CSDD									
	I	7.12±1.07	7.08±1.01	6.37±0.71	5.91±0.92	1	<0.0001	<0.0001	1.14	0.29	1.45
	II	7.25±1.15	7.04±1.16	6±1.02	5.33±0.86	0.34	<0.0001	<0.0001			
9		DEMQol									
	I	64.95±4.05	65.04±3.97	66.91±3.97	67.50±3.93	1	<0.0001	<0.0001	2.29	0.14	0.95
	II	63.54±3.32	63.75±3.31	66.25±3.28	67.33±3.11	1	0.04	0.001			

Fig 3. Effect of interventions on MMSE & ADAS Cog



Cognitive domains

Effects on 6 cognitive domains of MMSE showed significant change. Between groups out come analysis was assessed through independent sample t test, and it showed significant difference in orientation ($p<0.001$), language ($p=0.008$) and memory ($p=0.04$) favouring group II. Both groups showed improvements in orientation, concentration, memory recall, language domains of MMSE. In Orientation and concentration domains, significant improvement in group I and group II at 60th ($p<0.001$) and 90th day($p<0.001$) were noted. Memory recall domain, showed significant improvement in group I at 60th ($p<0.001$)and 90th day($p<0.001$) and group II at 60th ($p=0.02$) and 90th day ($p=0.01$). Significant improvement in group I at 60th ($p=0.02$), 90th day ($p=0.01$) and group II at 60th, 90th day($p<0.001$) in language domains were observed.

No changes were observed in Visuospatial and Working memory domains in both the groups.

Effect on cognitive domains of ADAS Cog was significant in clinical outcome analysis. *Brahmighruta* showed better improvements in memory (p=0.02) and language (p=0.04) domains of ADAS Cog. Both groups showed improvements in memory, language domains. In Memory domain, between groups out come analysis showed significant difference in memory (p=0.02) favouring group II. Within group significant improvement in group I and group II at 60th and 90th day(p<0.001) were noted. In Language domain, between groups out come analysis showed significant difference in language (p=0.04) favouring group II. Within group significant improvement in group I at 60th (p=0.001),90th day(p<0.001) and group II at 60th (p=0.002), 90th day(p<0.001).

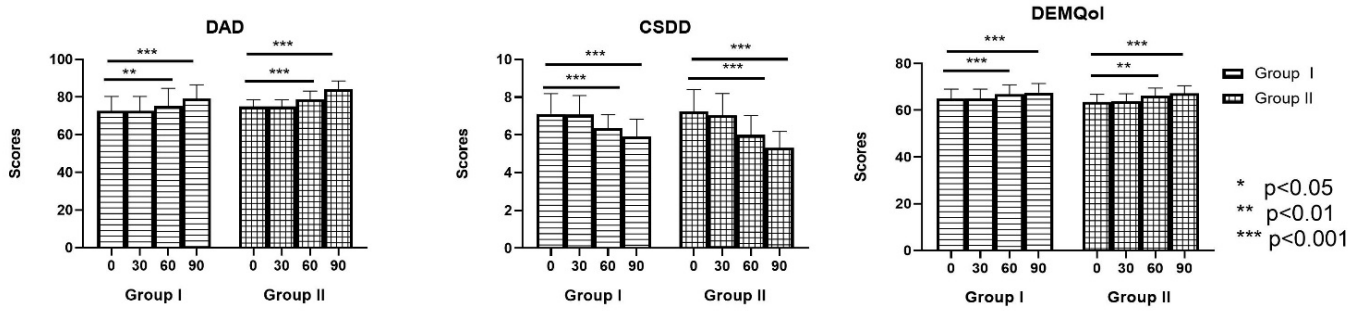
Praxis domain showed no significant change both between and within groups analysis.

Secondary Outcome

Between group comparison of interventions showed comparable effects in DAD (p=0.07), CSDD (p=0.29), DEMQol (p=0.14). Effect size was large in DAD (0.96), CSDD (1.45) and DEM Qol (0.95) favouring group II. Weight (p=0.14) and BMI (p=0.52) were comparable between groups. Effect size was medium in both weight (0.79) and BMI (0.75) favouring group II. (Table No 3) (Fig No 4)

Within group assessment in DAD, CSDD, DEMQol showed significant improvement at 60th, 90th day in both the groups. In DAD, group I showed improvements at 60th (p=0.005), 90th day (p<0.0001) and group II in 60th day, 90th day(p<0.0001). In CSDD, both the groups showed significant (p<0.0001) improvements at 60th and 90th day of interventions. In DEMQol, group I showed significant (p<0.0001) improvements at 60th and 90th day of intervention and group II showed significant improvements at 60th (p=0.04) and 90th (p=0.001) day of intervention. (Table No 3) (Fig No 4)

Fig 4. Effect of Interventions on DAD, CSDD and DEMQol

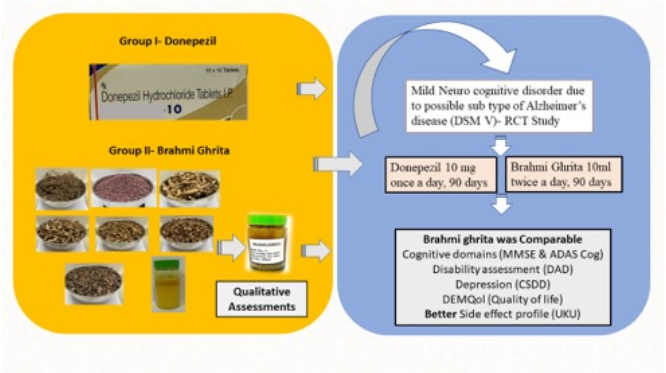


Disability assessment for dementia (DAD) has two major components. Basic ADLs (Activity of daily livings) or self care is addressed by 17 items and 23 items are related to instrumental ADLs. In basic ADL, between groups out come analysis showed no significant change. No changes in within group analysis in both the groups. In instrumental ADL, between groups outcome analysis showed significant difference in instrumental ADL (p=0.04) favouring group II. Within group significant improvement in group I and group II at 60th and 90th day(p<0.001) were observed.

Adverse events were assessed through UKU side effect scale. 8 patients in group I had mild adverse events of grade I. Autonomic adverse events were nausea (n=3) and giddiness (n=2). Other side effects were loss of appetite (n=3), difficulty in sleep (n=2) and headache (n=3). Duration of the side effects was from 1 to 4 days. Recurrent adverse events were noted and were mild. They did not interfere with the function of the patient and subsided with no additional medications. Group II reported no adverse events.

Discussion

Study showed that *Brahmighruta* was comparable to Donapezil in both primary assessment criteria like MMSE, ADAS Cog and also in secondary assessment criteria like DAD,CSDD, DEMQol. Donapezil produced mild adverse events in 8 patients and no adverse events were noted with *Brahmighruta* intervention. (Graphical abstract)



Patient profile showed that predominant participants were male (53.8%), middle class socioeconomic status, graduate level educated, vegetarian diet (73%), married (50%), *vataja prakruti* (40%), mean age was 69 yrs, mean duration of illness was 2.8 yrs. BMI, SBP and DBP were within the normative limits. MMSE showed to be in mild to moderate severity of cognitive impairment range (10-26 range).

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Brahmighruta showed improvements comparable to Donapezil. Both interventions showed improvements but scores remained in mild to moderate severity of cognitive impairment. *Brahmighruta* intervention showed increase in MMSE scores by 3.32 and 1.88 with Donepezil. Decrease in ADAS-Cog scores was by 3.16 with *Brahmighruta* intervention and Donepezil decreased by 2 scores. Neurocognitive disorders work group constituted during the process of DSM V, has accepted 6 principal domains of neurocognition that get affected in neurocognitive disorders. They are complex attention, executive function, learning and memory, language, perceptual–motor function, and social cognition. (37) MMSE evaluates 6 cognitive domains, namely visuospatial, language, concentration, working memory, memory recall and orientation. *Brahmighruta* showed better improvements in orientation, language and memory domains of MMSE. Both groups showed improvements in orientation, concentration, memory recall, language domains of MMSE. ADAS Cog evaluated 3 cognitive domains namely memory, language and praxis. *Brahmighruta* showed better improvements in memory and language domains of ADAS Cog. Both groups showed improvements in memory, language domains. DAD has two sub components, basic and instrumental activity of daily livings (ADLs). *Brahmighruta* showed better improvements in instrumental ADLs. However, both groups showed significant improvements with intervention in instrumental ADLs.

Brahmighruta has many herbal ingredients. Standardization of the current formulation was not done and is not available, however standardisation of an another formulation of *Brahmighruta* is reported. ([38]) Information on drug standardization of it's major ingredient, Bacopa monnieri is available. Major active principle of Bacopa monnieri having biological activity is steroidal tetracyclic triterpenoid saponin bacoside A. ([39]) A study ([40]) has developed HPTLC method for quality control determination of Bacoside A from Bacopa monnieri plant and its formulations. *Brahmighruta* in normal rats has shown to enhance learning and memory comparable to piracetam. (41) *Brahmighruta* could be effective because of it's various ingredients (Table no 4).

Table 4: Ingredients of Brahmi Ghruta

S. No	Sanskrit name	Latin name	official part	proportion
1	*Brahmi*	*Bacoppa monnieri (L.) Pennell*	Whole plant	32
2	*Vidanga tandula*	*Embelia Ribes Burm*	Seeds	4
3	*Vaca*	*Acorus Calamus Linn.*	Rhizome	2
4	*Guduci*	*Tinospora cardifolia Wall.*	Stem	2
5	*Haritaki*	*Terminalia chebula Retz.*	Fruit pericarp	12
6	*Vibhitaki*	*Terminalia bellerica (Gaertn.) Roxb.*	Fruit pericarp	12
7	*Amalaki*	*Emblica officinalis Gaertn.*	Fruit pericarp	12
8	Cow Ghee	Clarified butter		16

Extract of *Bacopa monnieri shown to have free scavenger activity, neuroprotective action on cells effected in AD like* prefrontal cortex, hippocampus, cholinergic neurons and striatum *against cytotoxicity and DNA damage. It ameliorates* anticholinesterase activity comparable to donepezil, rivastigmine, and galantamine. It decreases hippocampal β-amyloid deposition and stress-induced hippocampal damage. ([42]) Clinical studies have shown beneficial effect. standardized extract of *B monnieri* (Bacognize) 300 mg ([43]) twice a day for 6 months has shown improvements in MMSE in patients of AD. Butanol extract of *Tinospora cordifolia* prevented neuronal degeneration and showed neuroprotective action against glutamate. (44) Methanolic extracts of Acorus calamus roots inhibit acetylcholinesterase through the ingredients like essential oil β-asarone. (45) It prevented memory deficits and stress by controlling oxidative stress and inflammation process. (46) Acorus Calamus extract and its component α-asarone protect hippocampal cells from oxidative stress by decreasing reactive oxygen species production and endoplasmic reticulum (ER) stress by reducing phosphorylation of protein kinase RNA-like ER kinase signalling. (47) Through these mechanisms Acorus Calamus can have a potential role in management of AD. *Haritaki* (*Terminalia chebula* Retz) extract had potent antiamnesic effects through cholinergic modulation and anti oxidant activity in mice. (48) *Amalaki curṇa* (*Emblica officinalis* Gaertn) has memory enhancing, cholesterol lowering and anticholinesterase activity in mice. (49) *Triphala*, a polyherbal compound consisting of (Emblica officinalis (amalaki), Terminalia bellerica (*Vibhitaki*), and Terminalia chebula (*Haritaki*) is considered as *rasayana* (regenerative medicine) in Ayurveda and has antioxidant, anti-inflammatory, antiaging, hypolipidemic and antihyperlipidimic effect. (50) Embelin isolated from Embelia ribes Burm.f reversed amnesia and improved learning and memory in dose and time dependant manner on mice. (51) A review (52) has compiled the evidences of Ayurveda herbal drugs in Alzheimer's disease. This includes drugs like *ashwagandha* (Withania somnifera), *haridra* (Curcuma longa), *brahmi* (Bacopa monnieri), *shankhapuṣpi* (Convolvulus pluricaulis), *Mandukaparni* (Centella asiatica), *jyotiṣmati* (Celastrus paniculatus), *jaṭamaṃsi* (Nardostachys jatamansi) and *guggulu (Commiphora mukul)*. Mode of action of *Brahmighruta* and molecular mechanism is not fully understood but could be through their various active principles like Bacoside A and Bacoside B. Bacopa may act by reversing of cholinergic deficits in the frontal cortex and hippocampus (53), alleviates cholinergic neurodegeneration, decreases norepinephrine, and increase 5-hydroxytryptamine levels in the hippocampus, hypothalamus, and cerebral cortex.(54) *Acorus calamus* has the essential oil *β*-asarone, that inhibits acetylcholinesterase. (46) These drugs may act through reduction in inflammation and oxidative damage.(55) Ayurveda describes effects of ghee as memory enhancer, anti-inflammatory and anticonvulsant. (39)

Other herbal drugs have also shown to have a potential role in neuro degenerative disorders. Ginkgo biloba extract (EGb 761) effect on cognitively intact older adults showed improvement compared to placebo in neuro psychological measures. Methanolic extracts of Piper nigrum L. fruits decreases the oxidative stress in the rat hippocampus and ameliorates amyloid beta(1-42)-induced spatial memory impairment.(56) Other interventional studies on mild cognitive impairment/ Alzheimer's disease have also used ADAS cog and MMSE as the primary outcome measures. They have shown significant improvement compared to their comparator groups. MLC601, a natural neuroprotective medication intervention for 6 months compared with a placebo in Mild cognitive impairment (MCI) produced decrease by 2.26 in MMSE and increase by 3.82 (±6.16) for the ADAS-cog. In MLC601 groups, MMSE decrease was by 1.58 & 2.26 at 3rd and 6th month respectively. ADAS-cog increased by 1.65 at 3rd month and 3.83 at 6th month and were significant compared to control group.(57) Di-Huang-YiZhi (DHYZ) formula compared with aniracetam tablet (400 mg three times a day) in MCI for 12 months showed significant improvements in test group. MMSE increased by 1.02 and ADAS cog decreased by 2.88 in test group and were significant.(58) Chinese Herbal Formula compared with donepezil 5mg/day, 24 weeks, showed significant improvement in Chinese Herbal Formula group. Chinese Herbal Formula group produced MMSE increase by 1.29 (12 weeks), 2.18 (24 weeks). ADAS-Cog decreased by 0.6 (12 weeks) and 3.85 (24 weeks) and showed significant improvement. ([59]) A newly developed 6-month group-based multicomponent cognitive intervention in mild Alzheimer's disease and mild cognitive impairment patients compared to active control group (paper-pencil exercises), in a randomized controlled trial showed ADAS cog decrease by 1.4 points, MMSE increase by 0.1 points in test group and were significant. ([60]) Intravenous immunoglobulin (IVIG), administered in mild cognitive impairment due to Alzheimer's disease, showed significant improvement in test group. MMSE decreased by 0.71 in 12 months and ADAS-Cog increased by 0.4 in test group and were significant.(61) Above studies showed changes in MMSE at 3 months of interventions from 0.6 to 1.58 and in ADAS cog from 0.4 to 1.65. Current study showed higher improvements with *Brahmighruta* intervention (MMSE-3.32, ADAS cog-3.16) compared to previous studies. This could be due to usage of the newer diagnostic criteria or the better efficacy of the drug.

Study has notable components like randomized controlled design, 12 weeks study, donepezil as an active control, assessment through standard parameters like MMSE, ADAS-Cog, DAD,CSDD, DEMQol and UKU Side effect scale. Comprehensively assessing cognitive domains, depression, functional assessment measure, quality of life and adverse events. Further recommendations include a multi centric trial, larger sample size, longer duration of intervention, neuroimaging studies to exclude vascular, frontotemporal degenerative aetiology and demonstration of amyloid-β deposition in brain through PET study, biological assessments showing presence of mutations in the amyloid precursor protein gene (APP) or the presenilin genes (PSEN1 and PSEN2), assessment of amyloid-β and phosphorylated tau levels in cerebrospinal fluid etc. These would have helped in making the diagnosis to 'probable'. These are also the limitations of the study.

Conclusion

Brahmighruta showed efficacy in the management of Mild Neurocognitive Disorder due to possible Alzheimer's disease. *Brahmighruta* and Donapezil showed similar improvements in measures of cognitive domains, functional measures, depression, quality of life and had a better side effect profile. Due to lack of adverse effects *Brahmighruta* may be a preferred substitute for Donapezil. Hence *Brahmighruta* can play a role in the comprehensive management of Mild Neurocognitive Disorder due to possible Alzheimer's disease. Further studies on *Brahmighruta* are needed.

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