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A CLINICAL STUDY TO EVALUATE COMPARATIVE CLINICAL EFFICACY AND SAFETY OF BHC9612CP ON COGNITIVE FUNCTION IN ADULT SUBJECTS

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ABSTRACT

Background: Ashwagandha has been used since many years for improving Memory and Cognitive Functions in traditional medicine. In Ayurvedic medicine, Withania somnifera (Ashwagandha) is commonly being used for its broad spectrum of pharmacological actions. Ashwagandha is traditionally used as a rasayana (tonic) that works in a holistic manner to promote overall health and vitality. Ashwagandha is known for its memory boosting and restorative functions and is also reported to reverse loss of memory in by promoting the neurogenesis and growth of brain cells. Similarly root extract of the plant and one of its active component withanolide. A has been shown to improve spatial memory and cognitive deficits in temporal lobe epilepsy and experimental model of stroke. (Shaffi Manchanda et al. 2017). Ashwagandha extract has been suggested in the treatment of various neurological disorders due to its neuroprotective and anti-degenerative properties. Hence this clinical trial is conducted to evaluate the safety and efficacy of Ashwagandha extract in patients with memory impairment. **Objectives:** To evaluate comparative clinical Efficacy and Safety of BHC9612CP on Cognitive Function in Adult Subjects. **Conclusion**: After 56 days of treatment with Ashwagandha extract BHC9612CP there was significant improvement in MMSE scores. The safety results of this study demonstrated the formulation is safe and well tolerated when administered orally. Hence, from this study it can be concluded that Ashwagandha extract BHC9612CP favourably influences cognitive functions in memory impairment subjects and is safe orally.

KEYWORDS: Withania somnifera (L.) Dunal; ashwagandha; cognition; efficacy; memory; safety.

INTRODUCTION

Cognition is defined as ‘the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses. Cognition is the mental processes relating to the input and storage of information and how that information is then used to guide your behavior. It is in essence, the ability to perceive and react, process and understand, store and retrieve information, make decisions and produce appropriate responses. The modern word ‘cognition’ actually has its roots back to Latin, the word ‘cognoscere’ which is to ‘get to know’. With that in mind, cognitive functioning is therefore critical for day-to-day life, governing our thoughts and actions. We need cognition to help us understand information about the world around us and interact safely with our environment, as the sensory information we receive is vast and complicated: cognition is needed to distill all this information down to its essentials.

Cognitive decline is a common and feared aspect of aging. Cognitive impairment creates significant challenges for patients, their families and friends, and clinicians who provide their health care. (John E. Morley et al. 2015; Kenneth M. Langa et al. 2015) As populations continue to age, the prevalence of dementia is expected to increase. Alzheimer’s disease is by far the most common cause of dementia. The clinical course of dementia represents the challenges that this disease presents. There are no truly effective therapies for treating dementia, and the cost effectiveness of Cholinesterase inhibitors has been challenged. (Seema Joshi et al. 2006)

DESCRIPTION

Study Rationale - Ashwagandha extract has been suggested in the treatment of various neurological disorders due to its neuroprotective and anti-degenerative properties. Hence this clinical trial is conducted to evaluate the safety and efficacy of Ashwagandha extract in patients with memory impairment.

OBJECTIVES

The objective of this clinical study to evaluate comparative clinical Efficacy and Safety of Ashwagandha extract BHC9612CP in Cognitive Function in Adult Subjects.

METHODS

Inclusion Criteria

Both male and female subjects aged between 40-75 years with a complaint of memory impairment for at least one year without any major cognitive deficit. Subjects who are willing to sign ICF was enrolled in the study.

Exclusion Criteria

Patients having Psychiatric disorders, alcohol consumption, Subjects with any organ system infection in past 30 days, Subjects with severe cognitive problems like dementia, function disability, postvascular cerebral symptoms or with any neurological problems.

Study was conducted by Randomized, Parallel, Double blind, Placebo Controlled Clinical Study by Sri Venkateshwara Hospitals, Kuvempu nagara, BTM second stage, BTM layout, Bangalore- 560076. It involved in the clinical attendance of the subjects on recruitment and on follow –up. Subjects enrolled in the study received Study drug (from Baseline visit to 01 days –to Eot on day 56- The patients has taken Ashwagandha extract BHC9612CP.

The safety and efficacy parameters were compared with baseline and follow-up data with laboratory investigations, demographics were analyzed in the study. Adverse events / side effects were noted for each follow-up visits.

Ethics Committee Approval

All study related documents Protocol, Case Report Form, Dairy card, Investigator Brochure and Informed Consent Documents (English and Kannada Versions). Written Informed Consent was obtained from the subjects before the start of the trial and after due approval from IRB. Ethics Committee notifications as per the GCP guidelines issued by Central Drugs Standard Control Organization and Ethical guidelines for biomedical research on human subjects issued by Indian council of Medical Research has been followed during the Conduct of the Study (Clinical IEC-Institutional Ethics Committee for Ethics in Research and Approved on 21/01/2020).

Study Outcomes

Primary Outcomes

Change from baseline to the end of the study period in:

• Mini Mental State Examination

Secondary Endpoints

• Adverse events (AEs), frequency and severity.

• Changes in vital parameters and laboratory investigations

Disposition of Subjects

Total of 30 subjects

Group 1: Ashwagandha (15subjects)

Group 2: Placebo **(**15 subjects)

Description	No. of Patients
Screened	36
Enrolled	30
Screen failures	06
Completed end of study	30
Included in the safety analysis	30
Included in efficacy analysis	30

Visit Details

The patients were screened and enrolled. The enrollment day was considered as the baseline Day and the patient were in house till end of treatment visit on Day 56.

Statistical Analysis

The data generated in the clinical study will be analyzed by applying appropriate statistical method. Unless otherwise stated, all hypotheses will be tested at a significance level of 0.05 and 95% confidence interval. The Statistical analysis plan will also contain the rules and data handling conventions used to perform the analyses, and the procedure used for accounting for missing data.

RESULTS

In the study 30 patients were enrolled after meeting the inclusion Criteria and they are Randomised randomly into Test and Placebo. The enrolled subjects consisted of 15 males (50%) and 15 females (50%) participated in the study. Average BMI was 24.3 kg/m2, on the baseline visit. Clinical features of Cognitive impairment are evaluated in this study by MMSE scale and 11 parameters evaluated. There was significant improvement in the individual parameters in active group in comparison to placebo group. And there was also significant improvement in Total MMSE score from baseline to day 56 compared to placebo group.

Data sets analyzed

Efficacy Evaluation

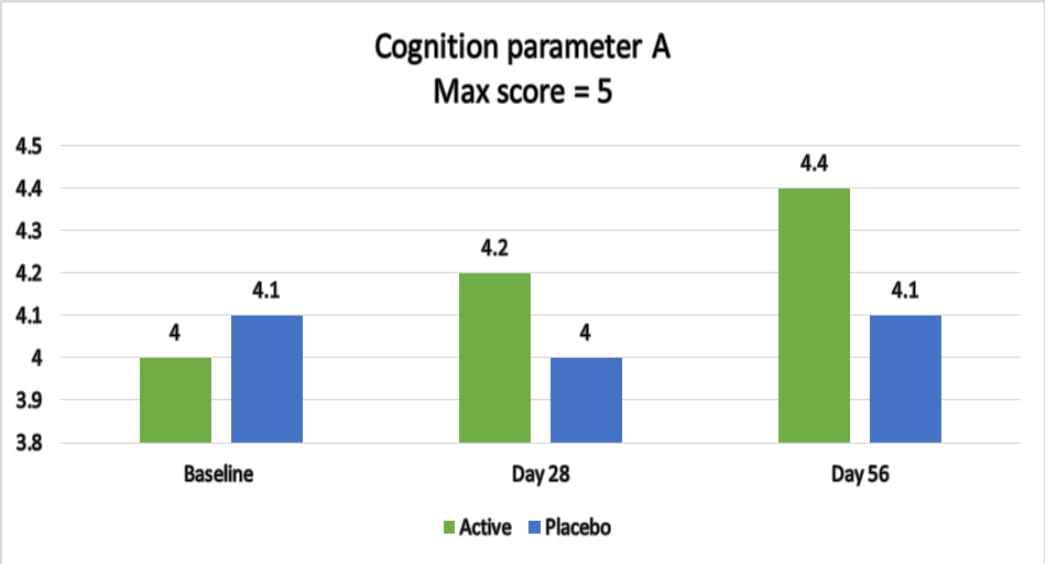
The Mini-Mental State Examination (MMSE) is the best-known and the most often used short screening tool for providing an overall measure of cognitive impairment in clinical, research and community settings. Clinical features of Cognitive impairment are assessed in this study by MMSE scale. The MMSE is composed of 11 major items (sub scales); A- temporal orientation (5 points), B- spatial orientation (5 points), C- immediate memory (3 points), D- attention/concentration (5 points), E- delayed recall (3 points), F- naming (2 points), G- verbal repetition (1 points), H- verbal comprehension (3 points), I- writing (1 points), J- reading a sentence (1 points), and K- constructional praxis (1 points). The MMSE has maximum score of 30, with five different domains of cognition analyzed: (1) Orientation, contributing a maximum of 10 points, (2) Memory, contributing a maximum of 6 points, (3) Attention and

calculation, as a measure of working memory, contributing a maximum of 5 points, (4) Language, contributing a maximum of 8 points, and (5) Design copying, contributing a maximum of 1 point. Individuals scoring two points below the maximum in any independent domain (except design copying) were considered to be impaired. (Kenta Shigemori et al. 2010; Faezeh Tatari et al. 2011; Ingrid Arevalo-Rodriguez. Et al. 2015). Improvement in MMSE score in sub scale score and overall total score signifies improvement in cognitive function and effectiveness of therapy.

MMSE Results: A- Temporal Orientation

In active group mean score was 4 at baseline and 4.4 at day 56. In placebo group score was 4.1 at baseline and 4.1 at day 56. There was significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.046)

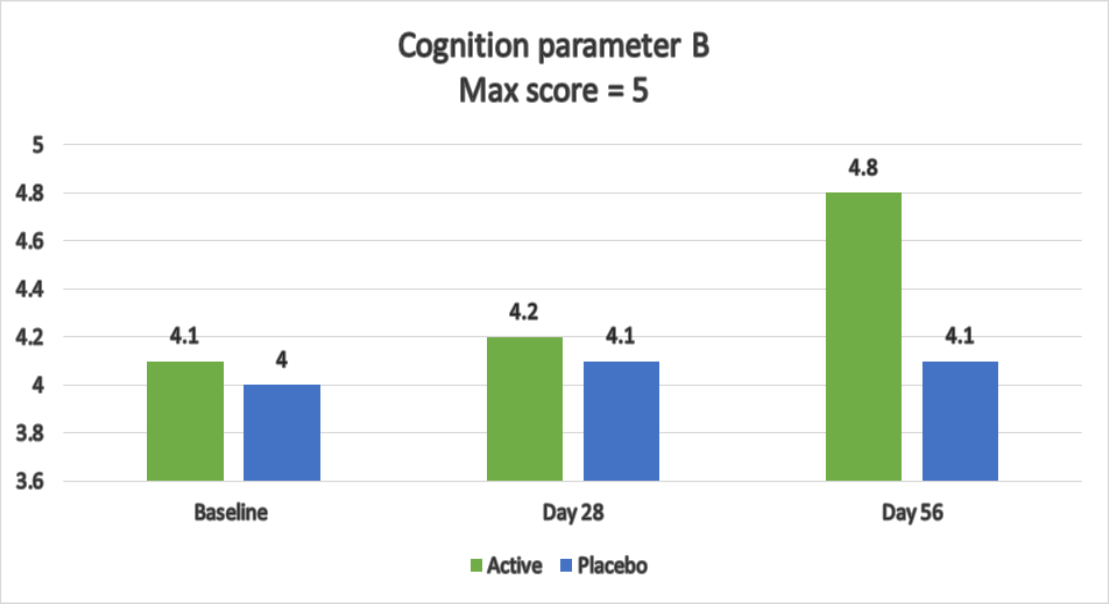
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)	P VALUE
A	Baseline	4	4.1	P value = 0.046
	Day 28	4.2	4	
	Day 56	4.4	4.1	



MMSE Results- B- Spatial Orientation

In active group mean score was 4.1 at baseline and 4.8 at day 56. In placebo group score was 4 at baseline and 4.1 at day 56. There was statistically significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.043)

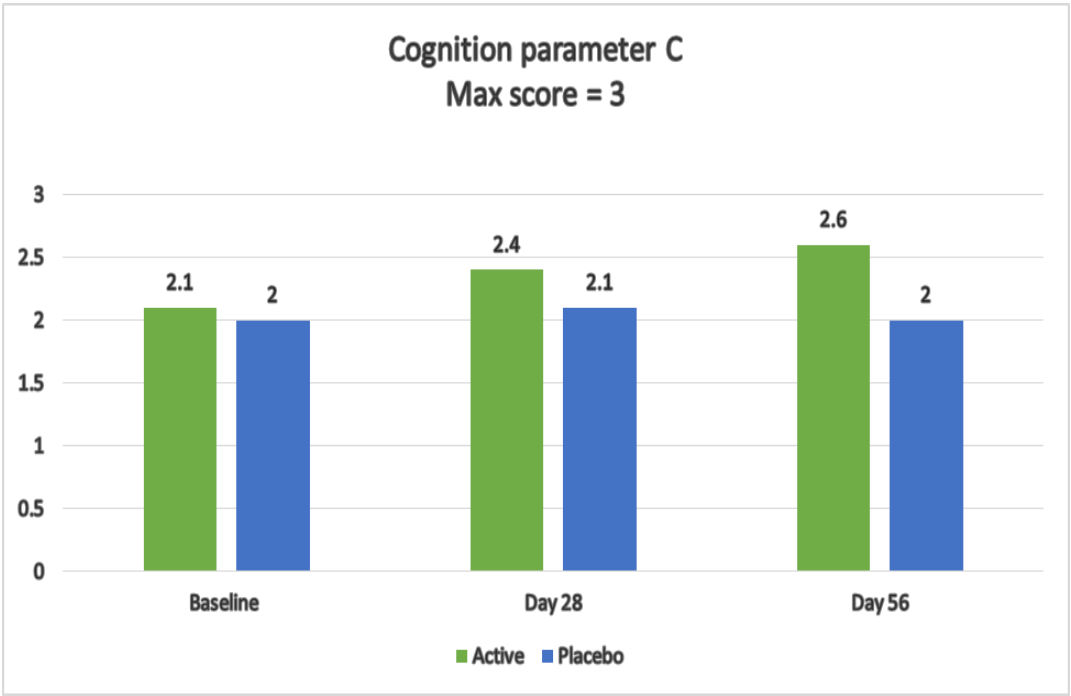
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)	P VALUE
B	Baseline	4.1	4	P value = 0.043
	Day 28	4.2	4.1	
	Day 56	4.8	4.1	



MMSE results- C- Immediate Memory

In active group mean score was 2.1 at baseline and 2.6 at day 56. In placebo group score was 2 at baseline and 2 at day 56. There was statistically significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.037)

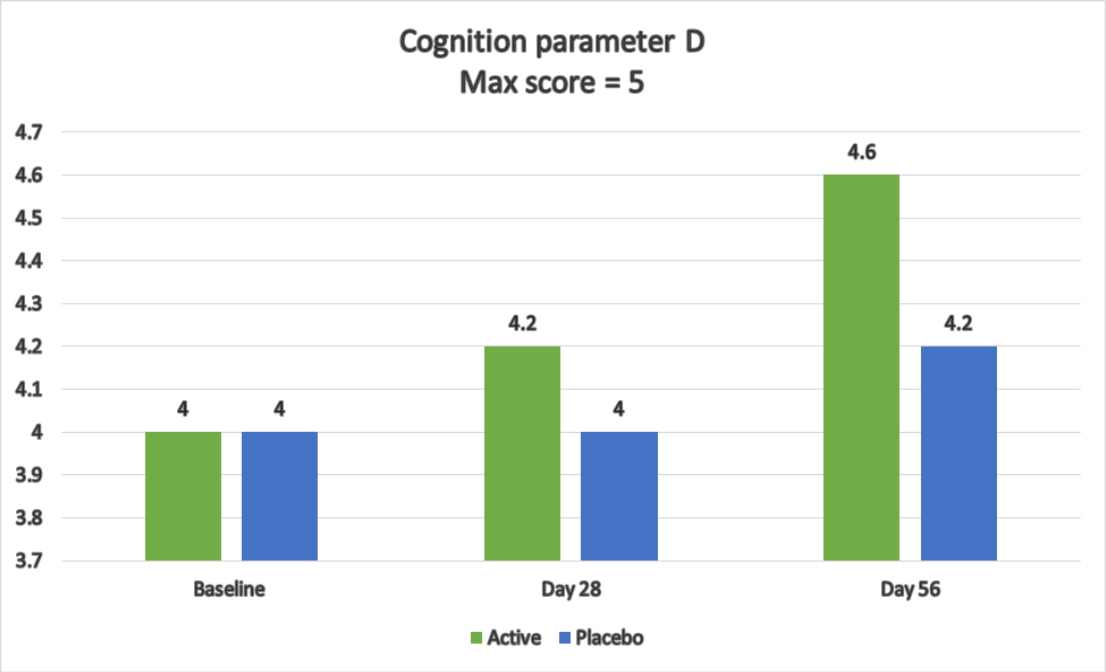
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)	P VALUE
C	Baseline	2.1	2	P value = 0.037
	Day 28	2.4	2.1	
	Day 56	2.6	2	



MMSE results: D- Attention/ Concentration

In active group mean score was 4 at baseline and 4.6 at day 56. In placebo group score was 4 at baseline and 4.2 at day 56. There was significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.047)

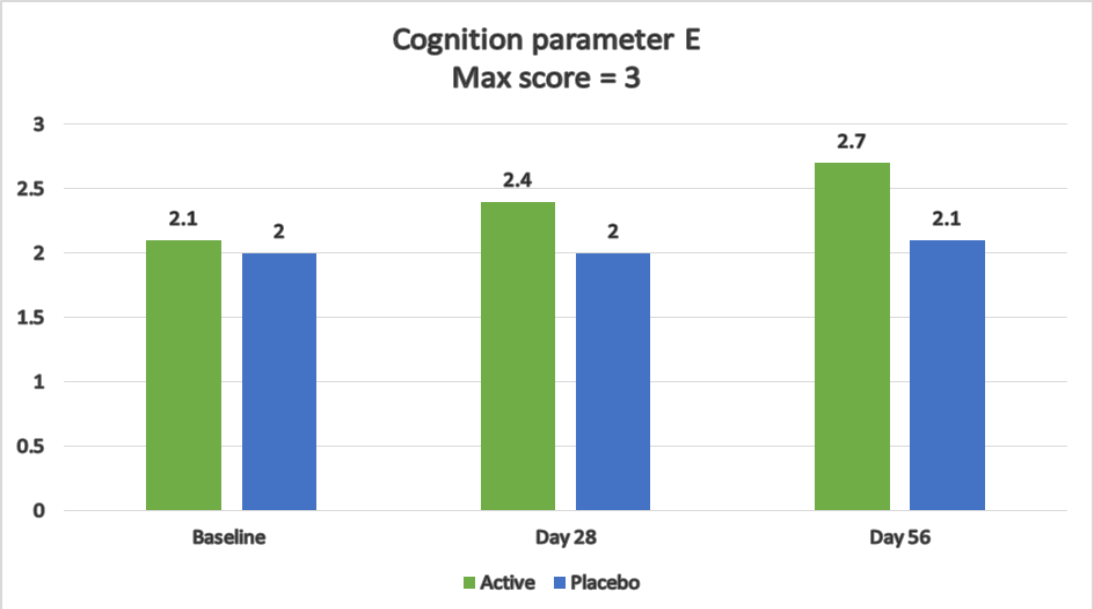
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)	P VALUE
D	Baseline	4	4	P value = 0.047
	Day 28	4.2	4	
	Day 56	4.6	4.2	



MMSE results: E- Delayed Recall

In active group mean score was 2.1 at baseline and 2.7 at day 56. In placebo group score was 2 at baseline and 2.1 at day 56. There was statistically significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.036)

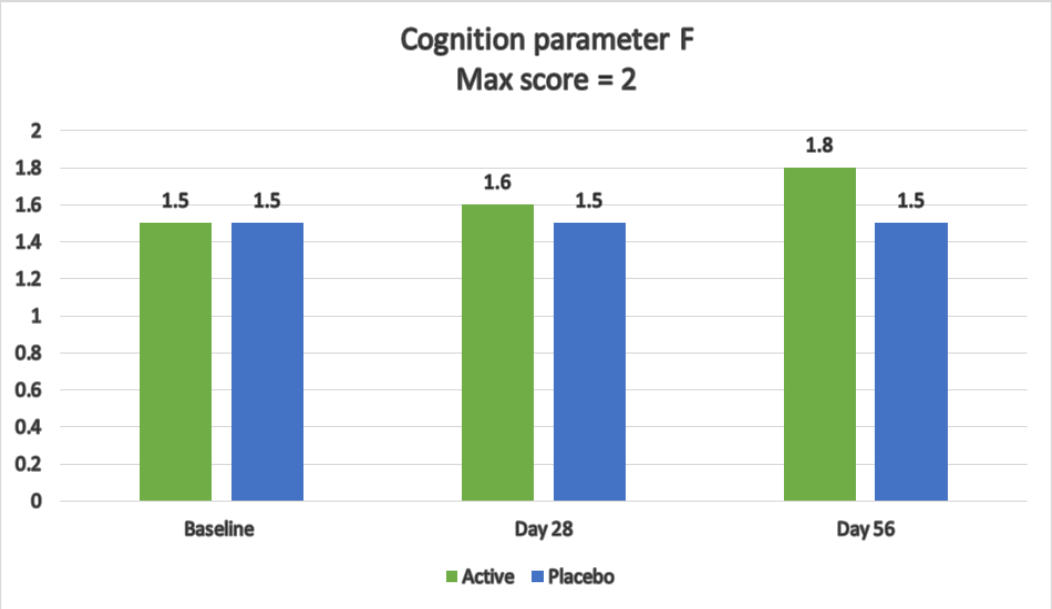
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)	P VALUE
E	Baseline	2.1	2	P value = 0.036
	Day 28	2.4	2	
	Day 56	2.7	2.1	



MMSE Results: F- Naming

In active group mean score was 1.5 at baseline and 1.8 at day 56. In placebo group score was 1.5 at baseline and 1.5 at day 56. There was significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.044)

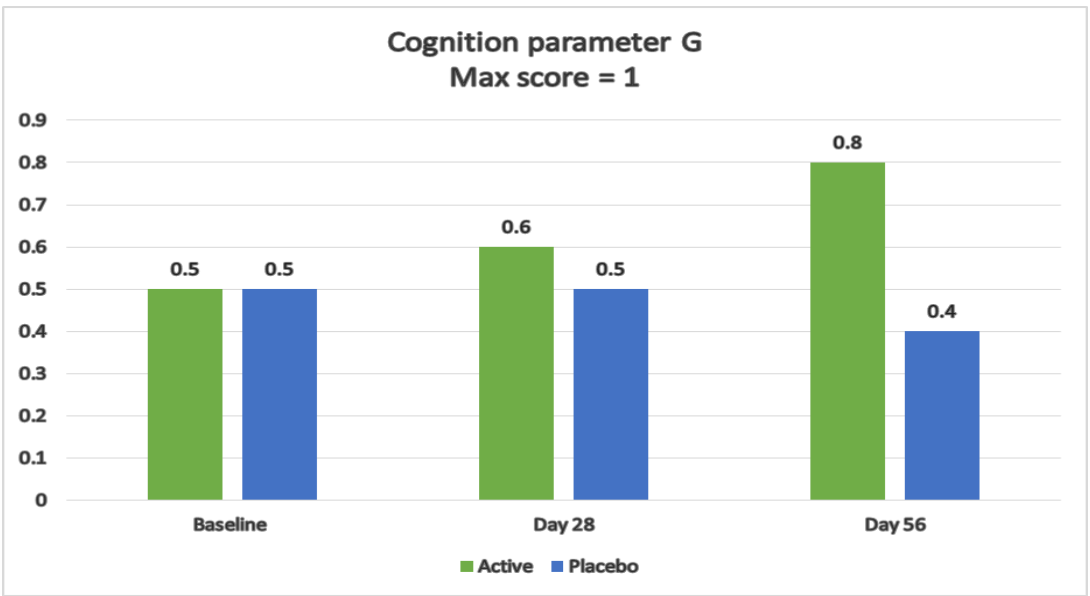
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)	P VALUE
F	Baseline	1.5	1.5	P value = 0.044
	Day 28	1.6	1.5	
	Day 56	1.8	1.5	



MMSE results: G- Verbal Repetition

In active group mean score was 0.5 at baseline and 0.8 at day 56. In placebo group score was 0.5 at baseline and 0.4 at day 56. There was significant improvement in mean score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.035)

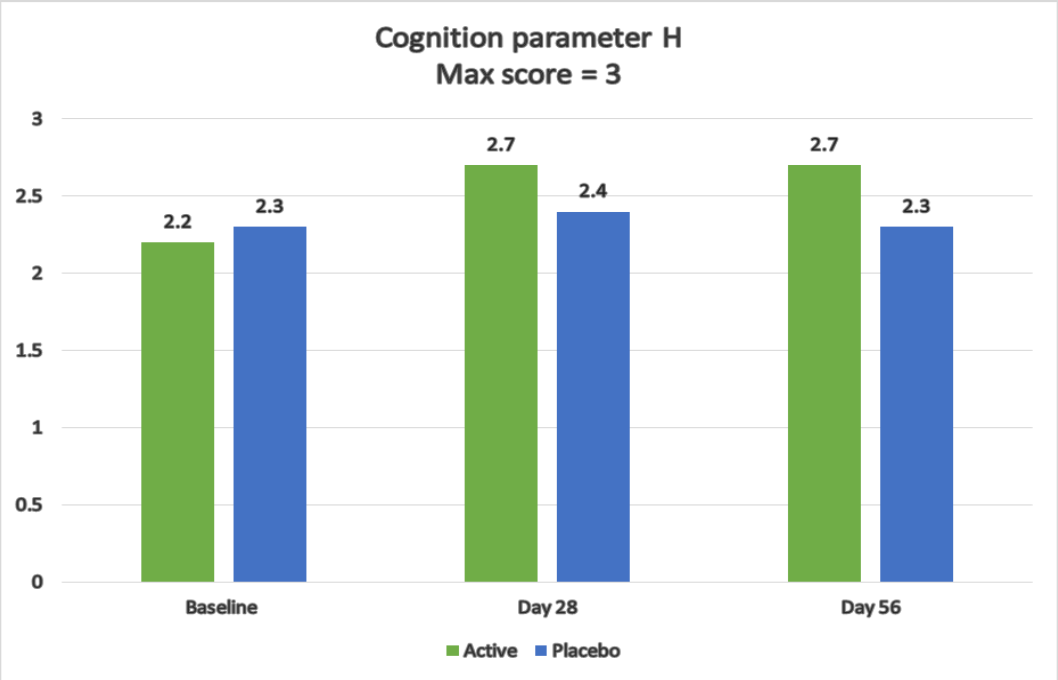
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)	P VALUE
G	Baseline	0.5	0.5	P value = 0.035
	Day 28	0.6	0.5	
	Day 56	0.8	0.4	



MMSE Results: H- Verbal Comprehension

In active group mean score was 2.2 at baseline and 2.7 at day 56. In placebo group score was 2.3 at baseline and 2.3 at day 56. There was significant improvement in score in active group from baseline to day 56 in comparison to placebo group (P value = 0.048)

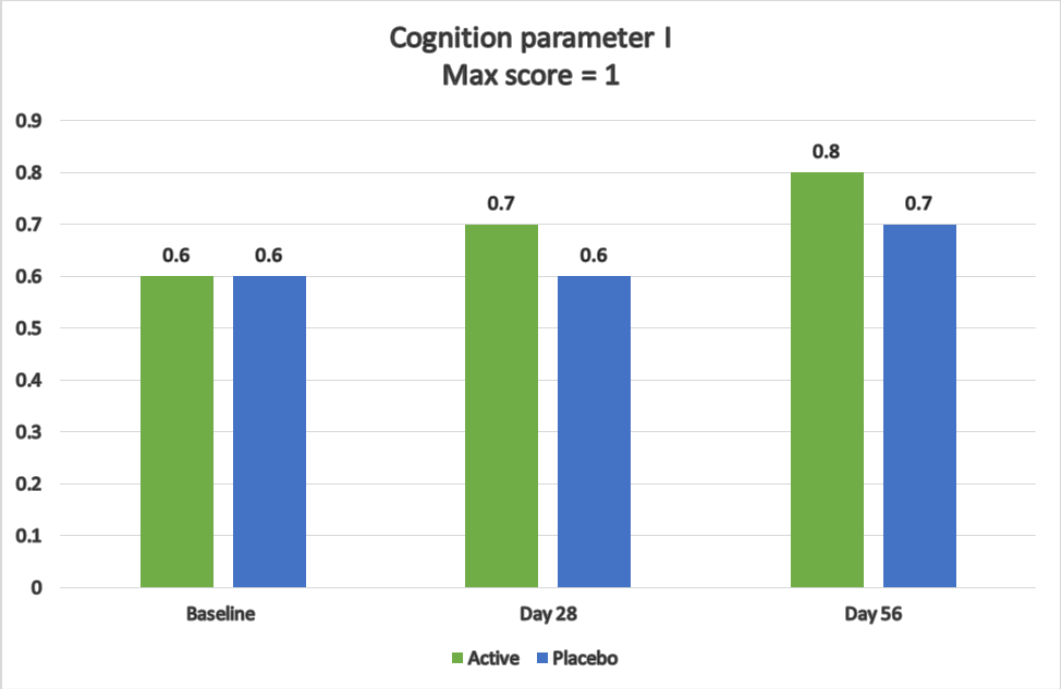
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)	P VALUE
H	Baseline	2.2	2.3	P value = 0.048
	Day 28	2.7	2.4	
	Day 56	2.7	2.3	



MMSE Results: I- Writing

In active group mean score was 0.6 at baseline and 0.8 at day 56. In placebo group score was 0.6 at baseline and 0.7 at day 56. There was improvement in score in active group from baseline to day 56.

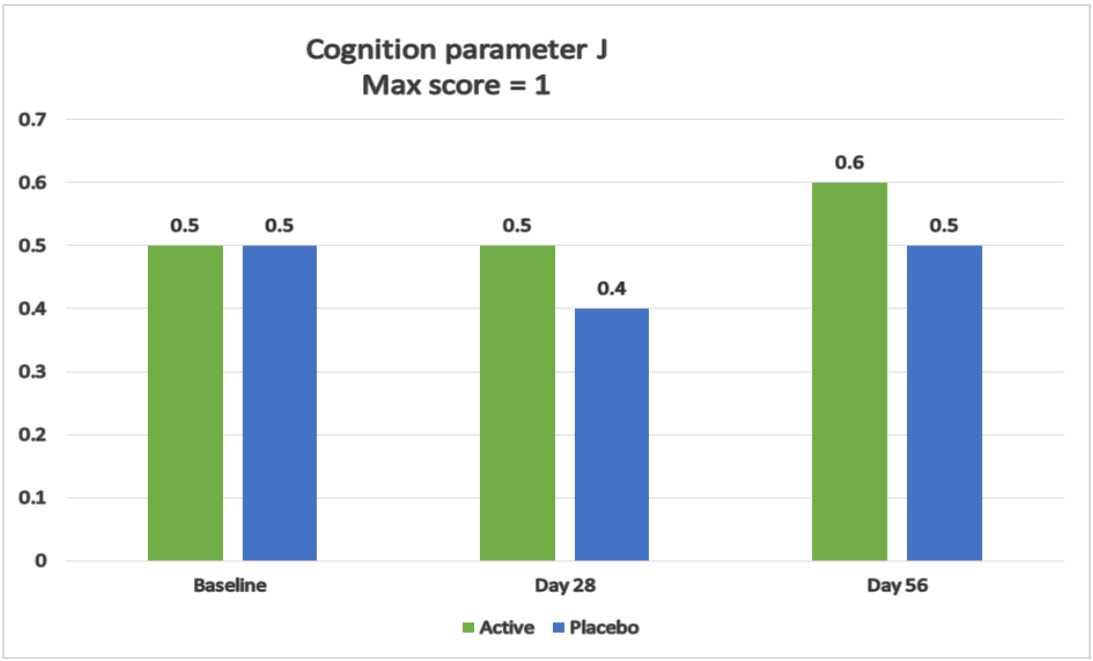
PARAMETER	VISITS	ACTIVE (mean score)	PLACEBO (mean score)	P VALUE
I	Baseline	0.6	0.6	P value = 0.086
	Day 28	0.7	0.6	
	Day 56	0.8	0.7	



MMSE Results: J- Reading a Sentence

In active group mean score was 0.5 at baseline and 0.6 at day 56. In placebo group score was 0.5 at baseline and 0.5 at day 56. There was improvement in score in active group from baseline to day 56.

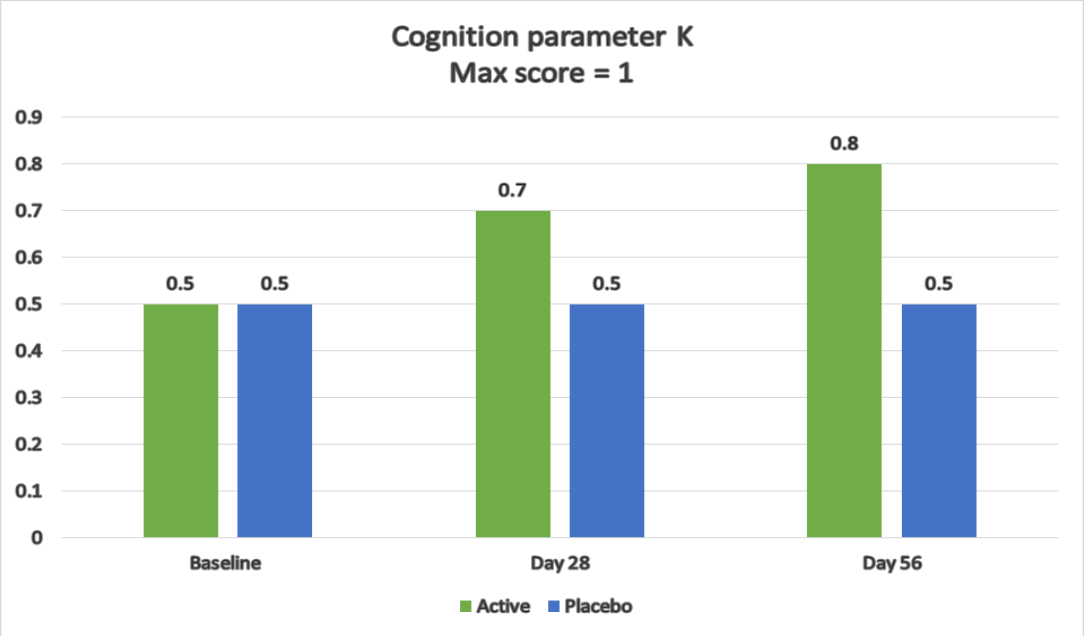
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)	P VALUE
J	Baseline	0.5	0.5	P value = 0.094
	Day 28	0.5	0.4	
	Day 56	0.6	0.5	



MMSE Results: K- Constructional Praxis

In active group mean score was 0.5 at baseline and 0.8 at day 56. In placebo group score was 0.5 at baseline and 0.5 at day 56. There was statistically significant improvement in mean score in active group from baseline to day 56 compared to placebo group. (P value = 0.049)

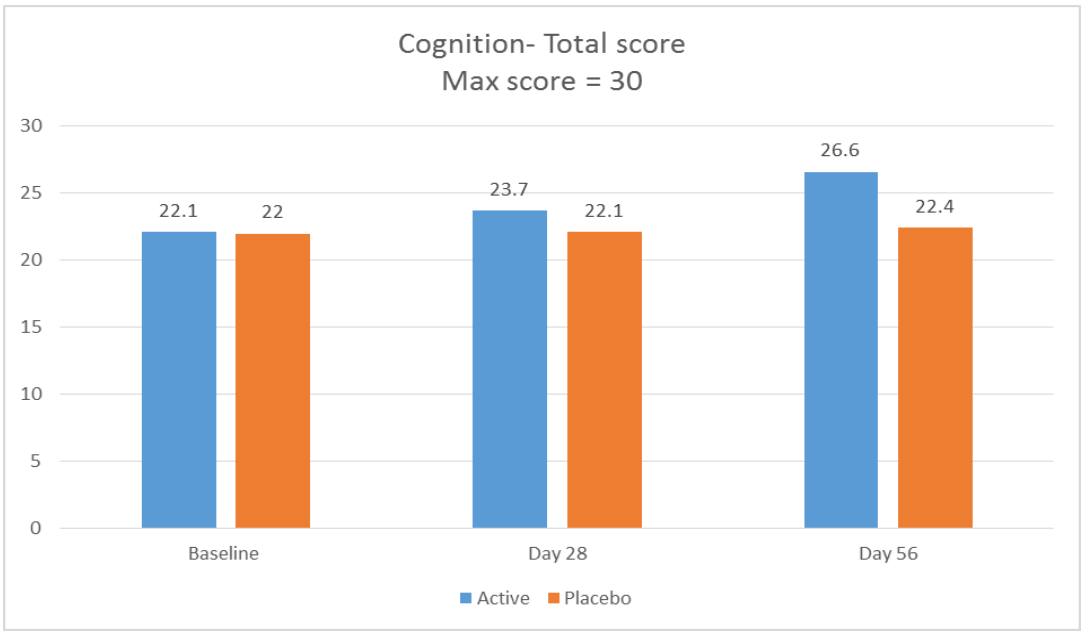
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)	P VALUE
K	Baseline	0.5	0.5	P value = 0.049
	Day 28	0.7	0.5	
	Day 56	0.8	0.5	



MMSE TOTAL SCORE

MMSE total score in active group on baseline was 22.1 and 26.6 on day 56. MMSE total score in placebo group on baseline was 22 and 22.4 on day 56. The improvement in MMSE total score in Active group from baseline to day 56 was statistically significant. (P value = 0.048) compared to placebo group.

PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)	P VALUE
TOTAL SCORE	Baseline	22.1	22	P value = 0.048
	Day 28	23.7	22.1	
	Day 56	26.6	22.4	



Safety Results

Vitals monitored and recorded at all the visits. There was no clinically significant abnormality observed in test and control group subjects inferring the active product is safe for administration. There were 4 adverse events (3 nausea, 1 head ache) observed for four different subjects which were categorized as mild to moderate in severity with none of the events were judged to be related to study product in the Investigator's opinion and 4 adverse effects (2 gastritis, 2 nausea) of mild to moderate severity were observed in placebo group and 4 adverse effects (2 gastritis, 2 nausea) of mild to moderate severity were observed in placebo group. All the adverse effects were managed by routine clinical measures. The safety parameters including ECG and laboratory tests (CBC, RFT and LFT) were within normal limits on screening and on day 56.

DISCUSSION AND CONCLUSION

The trial was conducted in Sri Venkateshwara Hospital, Bengaluru, Karnataka with Dr Poorna Prasad as Principal investigator, post its Institutional Ethics Committee approval /favorable opinion on the trial proposal.

The study was initiated on 13/02/2020and first subject was enrolled on 14/02/2020. There were a total of 6 screen failures and the last subject's last visit completed on 30-8-2020. All the 30 subjects were distributed equally between the two groups. A detailed examination at screening visit was done, MMSE assessment done and scores were measured between visits of all the enrolled subjects to check if there were any significant or clinically abnormal changes observed during the course of the treatment. Average age of subjects enrolled into the study was 57 years, approximately the same between both the groups at the time of screening. Total 15 males (50%) and 15 females (50%) participated in the study. Average BMI was 24.3 kg/m^2, on the baseline visit.

Detailed physical examination was performed on all the 30 enrolled subjects throughout all the 4 visits and none found to be abnormal. Vitals monitored and recorded at all the visits. There was no clinically significant abnormality observed in test and control group subjects inferring the active product is safe for administration. There were 4 adverse events (3 nausea, 1 head ache) observed for four different subjects which were categorized as mild to moderate in severity with none of the events were judged to be related to study product in the Investigator's opinion and 4 adverse effects (2 gastritis, 2 nausea) of mild to moderate severity were observed in placebo group. All the adverse effects were managed by routine clinical measures. The safety parameters including ECG and laboratory tests (CBC, RFT and LFT) were within normal limits on screening and on day 56. This infers that subjects who received active product did not show any clinically significant abnormality when compared to that of placebo group subjects. Therefore, it can be concluded that the active product in soft gel capsule formulation is completely safe for human oral consumption.

The Mini-Mental State Examination (MMSE) is a brief neuropsychological test that provides an overview of cognitive function which, in the setting of patients with mild cognitive impairment (MCI), is supplemented with more specialized neuropsychological tests for other domains of language, praxis and executive functions, among others. MMSE advantages reside in the easy way of administration (especially in terms of time and resources) without direct harmful effects, as well as a high acceptability by the health professionals involved in the management of people with dementia. In fact, this popular test is frequently administered by clinicians to MCI patients and our review could help them to interpret the results of MMSE of their patients. (Ingrid Arevalo-Rodriguez et al. 2015(3))

The MMSE facilitates the detection of mental status changes, particularly in the elderly, and thereby enhances patient care. A low score suggests cognitive impairment. (Faezeh Tatari et al. 2011) Improvement in MMSE scores on periodical assessment shows improvement in cognitive functions and guides therapy. Clinical features of Cognitive impairment are evaluated in this study by MMSE scale and 11 parameters evaluated. There was statistically significant improvement in individual parameters in active group in comparison to placebo group (A-Temporal orientation score: P value = 0.046, B- Spatial orientation: P value = 0.043, C- Immediate memory: P value = 0.037, D- Attention/concentration: P value = 0.047, E- Delayed recall: P value = 0.036, F-Naming: P value = 0.044, G- Verbal repetition: P value = 0.035, H- Verbal comprehension: P value = 0.048, K-Constructional praxis: (P value = 0.049). And there was also significant improvement in Total MMSE score from baseline to day 56 compared to placebo group. (MMSE TOTAL SCORE: P value = 0.048). Thus, this study evaluated the symptoms of different domains of cognitive functions and showed that the study drug BHC9612CP Ashwagandha extract improved the symptoms of cognition functions significantly. The therapy was well tolerated and all the participants completed the study duration. There were no significant adverse effects observed in the study.

CONCLUSIONS

Cognitive impairment/ dementia is a common progressive neurological disorder globally. Dementia refers to a clinical syndrome characterized by progressive cognitive decline that interferes with the ability to function independently in turn causes significant social and financial burden. BHC9612CP Ashwagandha extract has demonstrated an excellent safety and efficacy profile in patients with cognitive impairment in present study. Patients had clinically significant improvement in symptoms by day 56 as evidenced by MMSE scores in test group. Subscale parameters in MMSE scale were also improved

significantly in test group at the end of study indicating the improvement in symptoms of different domains of cognitive functions including naming, immediate memory, verbal comprehension, constructional praxis, delayed recall, temporal orientation, attention/ concentration and spatial orientation. Treatment was well tolerated and there were no any serious adverse effects related to study medication. This clearly indicates that BHC9612CP Ashwagandha extract is safe when administered orally and has definitive role in the management Cognitive impairment.

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