International Journal of Clinical Trials
Patel HR et al. Int J Clin Trials. 2016 Nov;3(4):267-273
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: http://dx.doi.org/10.18203/2349-3259.ijct20163966

Original Research Article

Clinical evaluation of the Dr. Brain syrup in the treatment of anxiety, depression, and dementia: randomized, placebo controlled, single blinded clinical study

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Received: 02 October 2016
Revised: 16 October 2016
Accepted: 17 October 2016

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ABSTRACT

Background: Epidemiological studies of Indian population show that dementia, anxiety, and depression are largely a major hidden problem in India. Ayurveda claims several plants are beneficial in cognitive disorders. The prime objective of study was to clinically evaluate polyherbal formulation (Dr. Brain syrup) and compare it with the Placebo. It was randomized, placebo controlled, single blinded clinical study, approved by Institutional Human Ethics Committee.
Methods: 60 outpatients from P. D. Patel Ayurveda Hospital (8-70 years) ready to sign Informed consent form were included in study. All these patients were given either Placebo syrup or Dr. Brain syrup at similar dose of 10 ml twice a day for 6 weeks. They were evaluated based on the HADS (hospital anxiety depression scale), EDQ (early dementia questionnaire) and symptoms assessment parameters on weekly basis.
Results: Result showed that there was significant reduction in HADS score at the end of the study. Moreover, the sensitivity and specificity of the HADS was observed highly relevant to detect the level of anxiety and depression by obtaining ROC curve. Numerical analysis of the EDQ was also shown eye-catching differences in patient receiving Dr. Brain syrup improved their memory at the end of the study compared to placebo group.
Conclusions: This study prooves the efficacy and safety of the Dr. Brain syrup in improving the memory and reducing the level of anxiety and depression in particular diseased patients without any side effects.

Keywords: Anxiety, Depression, HADS, EDQ, Memory enhancement

INTRODUCTION

Memory is the ability of an individual to record sensory stimuli, events, information, etc., retain them over short or long periods of time and recall the same at a later date when needed. Poor memory, lower retention and show recall are common problems in today's stressful and competitive world.[1] Various memory related disorders are classified nowadays amongst them Dementia is generally defined as the "Loss of intellectual abilities" (medically called cognitive dysfunction) of sufficient capacity to interfere with social or occupational functioning". The most common cause of dementia is Alzheimer's disease.[1] This disorders involves gradual memory loss, decline in the ability to perform routine tasks, disorientation, difficulty in learning, loss of language skills, impairment of judgment and personality changes, on the progression of the disorders, people become unable to care for themselves and the loss of brain cells eventually leads to the failure of other systems in the body.[2]

Anxiety is a human emotion that serves an adaptive function from a psychobiological perspective. However, in the psychiatric setting, feelings of fear or dread that are unfocused or out scale with perceived threat often require treatment.[3,4]

Epidemiological studies of Indian population reveal that dementia is largely a hidden problem in India. Ayurveda claims several plants are beneficial in cognitive disorders. Pharmaco-epidemiological studies reveal that herbal and allopathic learning and memory enhancing medicines are becoming very popular among Indian population.[5]

This study was planned to investigate the clinical efficacy and safety of the Dr. Brain syrup in the treatment of anxiety, depression and to improve memory. The investigational product, Dr. Brain syrup contain various extract of the herbal plants like ext. *Bacopa monnieri*, ext. *Convolvulus pluricaulis*, and ext. *Centella asiatica*.

Bacopa monnieri

The chemical constituents of Brahmi like Bacosides A and B, bacopasides I and II and bacopasaponin C and the extract of *Bacopa monnieri* exhibited antidepressant activity. Moreover, *Bacopa monnieri* was highly effective as an adaptogen, it normalized acute and chronic stress induced corticosterone changes in rats. It also normalized noradrenalin (NA), 5-HT, and DA in cortex and hippocampus of rats in acute and chronic unpredictable stress. Behavioral studies in animals have shown that Bacopa improves motor learning, acquisition and retention, and delay extinction of newly acquired behavior.[6,7]

Convolvulus pluricaulis

Convolvulus pluricaulis is one of the best and prominent natural medicines for improving memory due to its chemical composition, including phytonutrients like Scopoline ß-Sitosterol, convolvidine, subhirsine, convolvine, phyllabine, convoline and confoline. *Convolvulus pluricaulis* is mainly used as a brain tonic and brain stimulator.[8]

Centella asiatica

Aqueous extract of the herb showed significant effects on learning and memory and decreased the levels of norepinephrine, dopamine and 5-HT and their metabolites in the brain. *Centella asiatica* contains brahmicacid isobrahmic acid, brahminoside and brahmoside. It has psychotropic, sedative and anticonvulsant properties. It is also useful in dementia, mental disorders and anxiety.[9,10]

METHODS

This was a randomized, placebo controlled, single blind clinical study undertaken in 60 patients of both sex with age from 8 to 70 years of age diagnosed with Anxiety, depression, and have problems with memory in the P. D. Patel Ayurveda hospital, Nadiad. The patients were first randomized to 2 different groups, i.e. treatment group and placebo group, and evaluated with emphasis on the HADS questionnaire and EDQ questionnaire. Dr. Brain syrup was randomly administered to 30 patients at a dose of 2 teaspoonful to adults and 1 teaspoonful to children, twice daily for a period of 6 weeks, whereas the placebo was given to remaining 30 patients at a same dose for 6 weeks. The randomization code will be break down after the end of the study and Patient enrolled in Placebo group were treated with proper drug treatment after end of the trial. All the patients were followed-up for 1month.

The project was presented in Institutional Human ethics committee of J.S. Ayurveda Mahavidhyalaya and P. D. Patel Ayurveda Hospital and approval was obtained on 29th July 2015. This project is also submitted to Clinical Trials Registry of India on 09/05/2016 with the Registered No: CTRI/2016/09/007284.

Inclusion criteria

Patients willing to fill the Informed consent form, patients with both sex with the age starting from 8 years to 70 years of the age and patient suffering from the anxiety, depression and the memory loss are included for the study.

Exclusion criteria

Patients are not willing to submit Informed consent form,patients with hypertension, patients suffering from any ling term autoimmune disorder, patients with GI disorders and any other life threatening disorder are excluded from the study.

The objective of this study was to evaluate the benefits of Dr. Brain syrup in terms of the following parameters.

- Decrease in the hospital anxiety depression scale (HADS)
- Decrease in the early dementia questionnaire (EDQ)
- Perform the specificity and sensitivity of the level of anxiety and depression in patients, before and after the trial.

All the patients were examined and written informed consent was obtained at beginning of the study. The scoring of the symptoms was carried out by evaluating doctor oriented HADS and EDQ questionnaire at Initial, Intermediate and at the end of the trial.

Statistical analysis

Statistical analysis was carried out according to intention to treat principles. The changes in various parameters from baseline value and after 6 weeks were evaluated by paired t-test. The minimum level of significance was

fixed at 99% confidence interval and 2-sided p value of <0.0001 was considered highly significant.

Receiver operating characteristics (ROC) graphs are useful for organizing classifiers and visualizing their performance. ROC graphs are commonly used in medical decision making. The sensitivity and specificity of the HADS to distinguish the level of anxiety and depression will be obtained by getting the AUC.

RESULTS

After screening of the patients, 60 patients were enrolled (23 males, 37 females) for the study. All the patients were randomized through randomization.com, 1 block formula. Equal number of the patients was distributed in both the groups. 30 patients were randomized as control (placebo) group and remaining 30 patients were drug treatment (Dr. Brain syrup) group. No patients were complained for any adverse effects during and after the period of drug intake. Figure 1 and 2 demonstrates the age and gender distribution of the patients participated in the study.

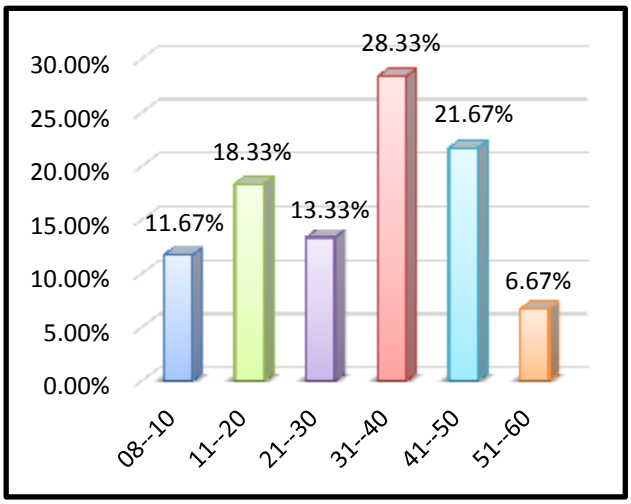

Figure 1: Percentage wise age group distribution.

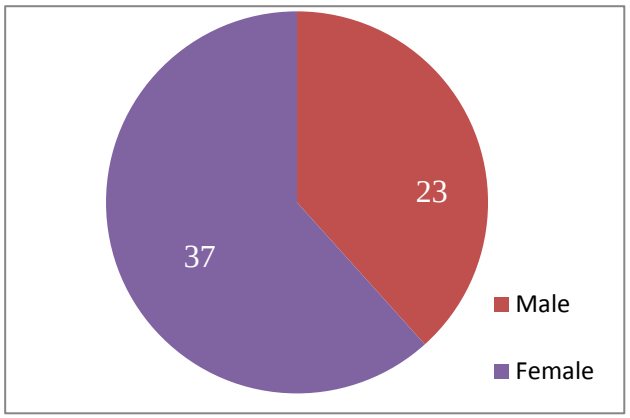

Figure 2: Gender wise distribution.

Table 1 presents the results of doctor oriented HADS questionnaire administered to the all patients. Anxiety level was identified in both groups at initial and end of the trial. Table 2 evaluates the depression level of the patients in both the treatment groups.

Table 1: HADS anxiety level evaluation in both groups.

Parameter	Treatment group		Placebo group	
	Before	After	Before	After
Mean	11.73	5.267	13.6	12.93
Std. Deviation	3.342	2.243	1.993	1.53
SEM	0.6101	0.4095	0.3639	0.2793
Lower 95% CI of Mean	10.05	4.138	12.6	12.16
Upper 95% CI of Mean	13.42	6.395	14.6	13.7
Mean of Differences	6.467		0.667	
99% Confidence interval	5.236 to 7.697		0.2852 to 1.048	
R squared	0.8785		0.4444	
t Value	14.48		4.817	
p Value	<0.0001		<0.0001	
P value Summary	Highly significant		Highly significant	

Table 2: HADS depression level evaluation in both groups.

Parameter	Treatment group		Placebo group	
	Before	After	Before	After
Mean	8.433	4.633	14.57	13.77
Std. Deviation	6.463	4.131	1.832	1.305
SEM	1.18	0.7543	0.3345	0.2382
Lower 95% CI of Mean	5.181	2.554	13.64	13.11
Upper 95% CI of Mean	11.69	6.712	15.49	14.42
Mean of Differences	3.8		0.8052	
99% Confidence interval	2.418 to 5.182		0.3948 to 1.205	
R squared	0.664		0.5053	
t Value	7.577		5.442	
p Value	<0.0001		<0.0001	
P value Summary	Highly significant		Highly significant	

Figure 3-6 represents the specificity and sensitivity of HADS in anxiety and depressed patients before and after the treatment in both the groups.

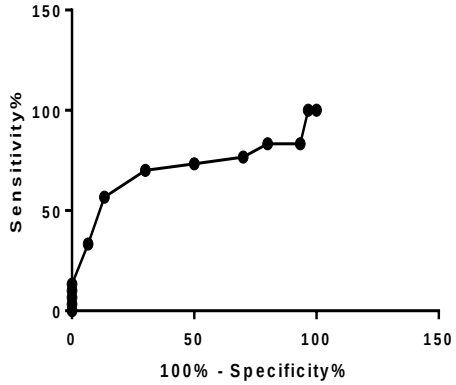

Figure 3: HADS_anxiety_placebo before vs. treatment before.

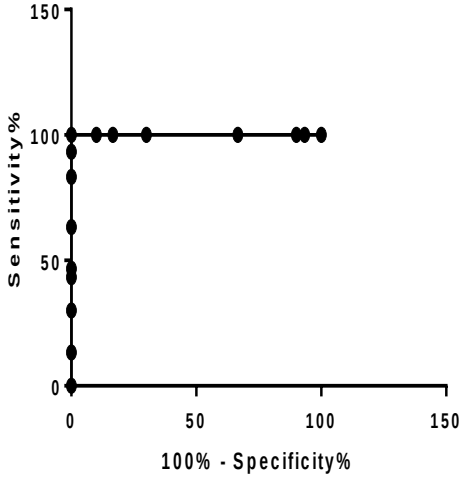

Figure 4: HADS_anxiety_placebo after vs. treatment after.

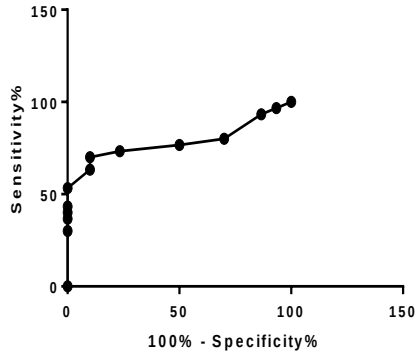

Figure 5: HADS_depression_placebo before vs. treatment before.

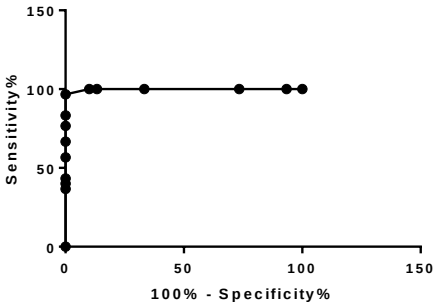

Figure 6: HADS_depression_placebo after vs. treatment after.

Table 3 and 4 represents the values of ROC graphs in anxiety and depressed patients involved in the study before and after treatment. All the patients were analyzed for the dementia by using EDQ and the questionnaire was modified by classifying the patients in to 4 categories according to severity of the symptoms, i.e. never, rarely, sometimes, and always in ascending way according to the severity of the symptoms. The severity of the symptoms was analyzed before and after basis in all categories as given in Table 5 and 6.

Table 3: ROC table for anxiety in HADS.

Treatment	ROC area	Standard error	P value
Placebo_anxiety_before v/s treatment anxiety before	0.6994	0.07193	=0.0080
Placebo_anxiety_after v/s treatment_anxiety_after	1.000	0.00	<0.0001highly significant at 95% CI

Table 4: ROC table for depression in HADS.

Treatment	ROC area	Standard error	P value
Placebo_depression_before v/s treatment depression before	0.7839	0.06451	=0.0002
Placebo_depression_after v/s treatment depression_after	0.9983	0.002538	<0.0001 highly significant at 95% CI

Table 5: EDQ assessment criteria in all weeks (treatment group).

Treatment group						
		No. of patients				
		Memory	Concentration	Physical Symptoms	Emotions	Sleep
Week 1	Never	0	0	8	9	9
	Rarely	0	5	4	1	6
	Sometimes	12	14	17	8	14
	Always	18	11	1	12	1
Week 4	Never	0	2	9	8	9
	Rarely	1	8	15	5	15
	Sometimes	20	16	6	13	6
	Always	9	4	0	4	0
Week 6	Never	0	8	17	11	19
	Rarely	9	16	12	9	11
	Sometimes	21	6	1	10	0
	Always	0	0	0	0	0

Table 6: EDQ assessment criteria in all weeks (placebo group).

Placebo group						
		No. of patients				
		Memory	Concentration	Physical Symptoms	Emotions	Sleep
Week 1	Never	0	0	1	3	6
	Rarely	6	1	1	4	6
	Sometimes	13	16	19	5	8
	Always	11	13	9	18	10
Week 4	Never	0	0	1	3	5
	Rarely	6	1	1	4	6
	Sometimes	12	15	17	6	9
	Always	12	14	11	17	10
Week 6	Never	0	0	1	3	3
	Rarely	6	2	1	4	4
	Sometimes	12	15	17	7	11
	Always	12	13	11	16	12

DISCUSSION

Result showed that, there was highly significant (p <0.0001) reduction in the HADS score in the treatment of anxiety and depression in Dr. Brain syrup treated group between 0 to 42 days treatment compared to placebo treated group as shown in Table 1 and 2.

To know the level of anxiety and depression in patients, receiver operating characteristic (ROC) curve is obtained on before and after treatment for anxiety and depression in both the groups. This curve plays a central role in evaluating diagnostic ability of tests to discriminate the true state of subjects, finding the optimal cut off values, and comparing two alternative diagnostic tasks when each task is performed on the same subject.[11] In this Study, Placebo group was considered as the Control group and compared with the drug treatment group on before and after the trial to discriminate the caseness and non-caseness of the patients. An AUC value of 0.50 reflects a test that is unable to discriminate between cases and non-cases, while a value of 1.00 means perfect sensitivity and specificity at all cut-off values.[12] Before trial, both the group of patients were untreated, received no treatment. Hence, the AUC of the curve was found not significant which means HADS considered all patients with similar symptoms of the disease without any difference. But after the specific drug treatment, this curve was found highly significant at the end of the trial, when compared the treatment group to control group. This result shows the capability of the HADS scale to distinguish the level of anxiety and depression in before and after the trial and identify the level of symptoms in patients. The AUC (area under curve) of anxiety, before the 6 week of treatment was found 0.6994 (p =0.0080 at 95% CI) which turned to 1.000 (p <0.0001 at 95% CI) after the 6 week of treatment. It shows that, the sensitivity and specificity of HADS questionnaire was extremely high to detect the anxiety treated patients. Similarly, the depression rate of the ROC was also found 0.7839 (p

=0.0002 at 95% CI) and 0.9983 (p <0.0001 at 95% CI) in before and after treatment respectively. These AUC results proves the perfect sensitivity and specificity of the HADS and Dr. Brain syrup to discriminate the patients between drug treated and placebo and proves the efficacy of the drug in both anxiety and depression.

Moreover, all the patients were also analyzed for the dementia by using EDQ and the questionnaire was modified by classifying the patients in to 4 categories according to severity of the symptoms, i.e. never, rarely, sometimes, and always in ascending way according to the severity of the symptoms. The severity of the symptoms was analyzed before and after basis in all categories. 21.8% of patients had problems with memory at always or sometimes basis before treatment. This ratio was observed to 22.4% after the treatment where the severity was shifted to the never or rarely categories for all the patients. This result shows the 102.75% of improvement in the severity of symptoms of the memory in treatment group. While this ratio of improvement in symptom was found only 20.86% in placebo group as shown in Table 5 and 6.

Memory does improve with age. As persons grow they use their experiences to establish, elaborate meaningful relations in the information to be remembered, as a consequence, to remember more accurately.[13,5] Our result have shown that there was a significant improvement in the patients suffering from the anxiety and depression after the treatment with Dr. Brain syrup. The sensitivity and specificity of the HADS questionnaire to measure the level of the anxiety and depression was also found highly significant after the treatment with Dr. Brain syrup through obtaining the ROC curve. It also boosts the memory power and concentrations to the younger age patients and also helped to patients with older age to improve their memory.

CONCLUSION

Our data suggest that, Dr. Brain syrup improves memory as compared to placebo in patients. It also helps to improve the level of anxiety and depression. Dr. Brain syrup might be reducing the level of anxiety and depression by normalize the Noradrenaline, 5-HT, and dopamine. The presence of scopoline, β-sitosterol, bacoside A & B, convolvidine, brahmin side and brahmoside helps to improve the memory power.

In conclusion, this study authenticate efficacy and safety used to improve the memory and reducing the level of anxiety and depression in particular diseased patients. However, group of patients in placebo group also showed some moderate change in the level of anxiety and depression due to effect of psychological factors. There is no sign of any serious adverse effect identified during the study. Hence, Dr. Brain syrup received the momentum to treat anxiety, depression and also helps to improve the memory without any serious effect.

ACKNOWLEDGEMENTS

Entire project was sponsored by "Petlad Mahal Arogya Mandal Pharmacy". Dr. Brain syrup was prepared at the Production department of above organization and supplied to P. D. Patel Ayurveda Hospital, NADIAD. I would like to thank and congratulate Dr. Kalapi Patel for helping and completing this entire Project in the Hospital.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee for Human Research of J. S. Ayurveda Mahavidhyalaya and P. D. Patel Ayurveda Hospital, Nadiad has reviewed and approved the project with CTRI Register No: CTRI/2016/09/007284

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Cite this article as: Patel HR, Patel K, Patel M, Gupta SN, Patel J, Patel P, Patel A. Clinical evaluation of the Dr. Brain syrup in the treatment of anxiety, depression, and dementia: randomized, placebo controlled, single blinded clinical study. Int J Clin Trials 2016;3(4):267-73.