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A SINGLE BLIND, PLACEBO CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF HERBOKAM® PLUS CAPSULES (AN AYURVEDIC FORMULATION) IN THE PATIENTS WITH STRESS INDUCED INSOMNIA

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ABSTRACT

Stress and allied symptoms are now a common cause for variety of neurological disorders and hypertensions etc. modern remedies has more hazards and habit forming. Present single blind, placebo control study was aimed to analyze effect of herbal remedy Herbokam plus capsule of Unijules Life Sciences ltd for stress induced insomnia. Carried out in Dr. D.Y. Patil college of Ayurved, hospital and research centre. Patients aged between 18-75 years with symptoms of stress induced insomnia were randomly enrolled by proper inclusive and exclusive criteria, and placed in a trial and placebo group and given a dose of 2 capsules at bed time. Primary efficacy parameters were analyzed by sleep scales of Insomnia severity index, Epworth sleepiness scale and MOS Sleep scale, and safety was assessed by the adverse events noted during the study and use of rescue medications used during the study. Out of 186 patients enrolled in the study 178 patients (89 in either group) completed the 8 weeks treatment. Highly significant difference was observed after 4th week of treatment in herbokam plus group where as no significant difference was noted in placebo group and significant difference is observed between the two groups which states that herbokam plus is an effective remedy for the symptoms of stress induced insomnia if given for 4 to 6 week duration.

Keywords: Herbokam plus, Unijules Life Sciences Ltd. Stress, Insomnia

INTRODUCTION

Stress in humans results from interactions between persons and their environment that are perceived as straining or exceeding their adaptive capacities and threatening their well-being.

The element of perception indicates that human stress responses reflect differences in personality, as well as differences in physical strength or general health. [1,2]

Risk factors for stress-related illnesses are a mix of personal, interpersonal, and social variables. These factors include lack or loss of control over one's physical environment, and lack or loss of social support networks. People who are dependent on others (e.g., children or the elderly) or who are socially disadvantaged (because of race, gender, educational level, or similar factors) are at greater risk of developing stress-related illnesses. Other risk factors include feelings of helplessness, hopelessness, extreme fear or anger, and cynicism or distrust of others. [3,4]

Insomnia is a symptom of several sleep disorders, characterized by persistent difficulty falling asleep or staying asleep despite the opportunity. Insomnia is a symptom, not a stand-alone diagnosis or a disease. By definition, insomnia is "difficulty initiating or maintaining sleep or both" and it may be due to inadequate quality or quantity of sleep. It is typically followed by functional impairment while awake. Both organic and non-organic insomnia without other cause constitute a sleep disorder, primary insomnia. [5]

The pattern of insomnia often is related to the etiology. Insomnia affects 1 in 33 people. Poor sleep quality can occur as a result of sleep apnea or clinical depression. Poor sleep quality is caused by the individual not reaching stage 4 or delta sleep which has restorative properties. Between 10% and 30% of adults have insomnia at any given point in time and up to half of people have insomnia in a given year. About 6% of people have insomnia that is not due to another problem and lasts for more than a month.[12,13]

A Herbokam Plus capsule is a balanced blend of extracts of Ashwagandha (Withania somnifera), Jatamansi (Nordostachus jatamansi) and Brahmi (Bacopa moonieri) in optimum concentration that help to combat restlessness and stress. They help in fighting stress naturally and maintain a healthy nervous system. They are natural adaptogen and help support a person's natural physical and mental ability to fight daily stress. This is an ideal formula for anxiety, stress, depression and tiredness.

MATERIALS AND METHODS:

This study was a single blind; placebo controlled involving patients with Stress Induced Insomnia. Each patient has received a single treatment of either investigational product Herbokam plus or a placebo drug. The goal was to enroll approximately 200 patients in order of 150 patients complete the trial and provide data for analysis.

Study was carried out in Dr. D.Y. Patil Ayurved College, hospital and research centre. Prior approval from institutional ethics committee is taken by submitting protocols, CRF and all relevant data to IEC.(IEC no. PDDYPU/1361/2010)

The patients were evaluated for time to resolution of signs and symptoms of sleep scales over the 8 week of treatment by clinical/physical evaluation of the symptoms by the investigator. Additionally, during the 8-week of treatment period, the two groups were assessed for any adverse events at each visit and use of rescue medication used by the patients during the therapy.

INCLUSION AND EXCLUSION CRITERIA:

Inclusion criteria: Patient should age between 18-70 years; should have confirmed diagnosis of Stress induced Insomnia, should be free of all antidepressants and benzodiazepine for two weeks. History of the following for at least 3 months prior to the screening visit: Usual reported subjective total sleep time (TST) 3 hours. Usual sleep disturbance with a subjective sleep onset latency of > 30 min. Daytime complaints associated with poor sleep (e.g., fatigue, irritability, difficulty in concentrating). Patient must sign informed consent prior to any study-mandated procedure and willing to comply with daily protocol.

Exclusion criteria: Subject aged more than 70 years and less than 18 years of age, been in more than 2 studies in the past 2 years. Active suicidal ideation or active psychosis, as this may present a concern regarding safety for a subject's participation in this study; Alcohol use > 14 beverages/week, as this may impact on response to the intervention and assessment measures. Active malignancy, autoimmune condition, or treatment with immunosuppressive drugs; Active involvement in any psychotherapy or need of immediate psychiatric (e.g., imminently suicidal patients) or medical care (e.g., patients with acute cardiac symptoms), or have attempted suicide in the past 6 months. And those not willing to sign informed consent were excluded from the study.

STUDY PROCEDURE:

Screening Visit: The initial screening was performed 3 days prior to enrollment. At this visit informed consent, medical history and patient demographics were obtained. Formats for the same (ICF, CRF) was approved previously by the independent ethics committee; physical examination, vital signs assessment (temperature, blood pressure, pulse, and weight) and nutritional evaluation were performed;

Visit V1 (3 days after screening): The patients who were eligible were entered in a 8 weeks active treatment period. Thereafter, they were allowed to take the medicine to home for further doses which was two capsules at bed time. At OPD visit, parameters of INSOMNIA SCALES [14] were measured using efficacy assessment criteria for Symptom Score.

Follow Up Visits: Patients were examined on the Week 2, Week 4, Week 6 and Week 8 Study Visits thereafter until 100% resolution of signs and symptoms. At each study visit symptom score assessment was done and patient was observed for any adverse reactions etc.

EFFICACY PARAMETERS:

Each patient was assessed for symptoms score decided as efficacy parameters for Insomnia. The symptoms score assessment was done by assessment on the internationally accepted scales of Insomnia severity index, Epworth sleepiness scale and MOS Sleep scale.

Safety was assessed on the basis of no of adverse events noted during the study and use of rescue medicines consumed during the study.

ADVERSE EVENTS:

All adverse events reported or observed by patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requir-

ing specific treatment. For patients withdrawing from the study, efforts were made to confirm the reason for withdrawing.

STATISTICAL ANALYSIS:

Statistical analysis is done using paired 't' test for paired data within group and unpaired 't' test to analyze data between the groups. The criteria for statistical significance was $p<0.05$. Descriptive statistics are presented for all measurements of efficacy. Categorical data are summarized and presented using frequency tables of counts, histograms, and percentages. Continuous variables are summarized and presented as means, standard deviation, medians, and ranges.

OBSERVATIONS AND RESULTS:

210 patients are screened for the trial from which 186 patients were enrolled in the study. From the total enrolled patients 178 patients (89 patients in either groups of trial drug and placebo) completed the 8 weeks treatment period remaining patients discontinued the study.

In case of Insomnia severity index significant result was observed in mean of treatment group after 2 weeks of treatment and highly significant results after 4, 6 and 8 weeks of treatment as compared to before treatment, where as no significant results was noted in placebo group after 2, 4, 6, and 8 weeks. (Graph 1.1)

In case of Epworth sleepiness scale no significant results was observed after 2 and 4 weeks of treatment (compared with before treatment) in case of treatment group, but after 6 week of treatment highly significant result was observed and after 8 week of treatment highly significant results was noticed. Where as in case of placebo group no significant results were observed in any week compared with baseline. (Graph 1.2)

In case of MOS sleep scale highly significant results were noticed after 6 and 8 week of treatment where as no significant results were observed after 2 and 4 weeks as compared with baseline values. (Graph 1.3)

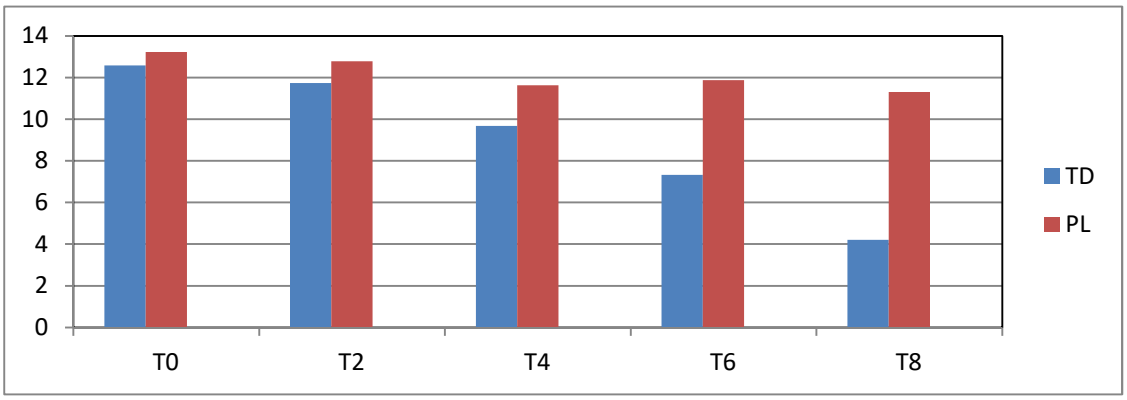
Highly significant difference was observed between test drug HERBOKAM PLUS and PLACEBO which states the effect is due to the test drug.

TABELS AND GRAPHS:

Table 1.1: Showing effect of Test drug (Herbokam plus) and Placebo on Insomnia severity index

Insomnia Severity Index						
Visit		T0	T2	T4	T6	T8
Mean	Test drug	12.58	11.73	9.68	7.32	4.22
	Placebo	13.22	12.78	11.62	11.88	11.31
SD	Test drug	2.32	2.51	2.64	2.61	2.31
	Placebo	2.36	2.44	2.48	2.21	2.36
SE	Test drug	0.30	0.33	0.34	0.33	0.29
	Placebo	0.36	0.35	0.33	0.33	0.30
P- value	Test drug		>0.05 (NS)	<0.001(***)	<0.001(***)	<0.001(***)
	Placebo		NS	NS	NS	NS

Graph 1.1 showing effect of Test drug (Herbokam plus) and Placebo on Insomnia severity index

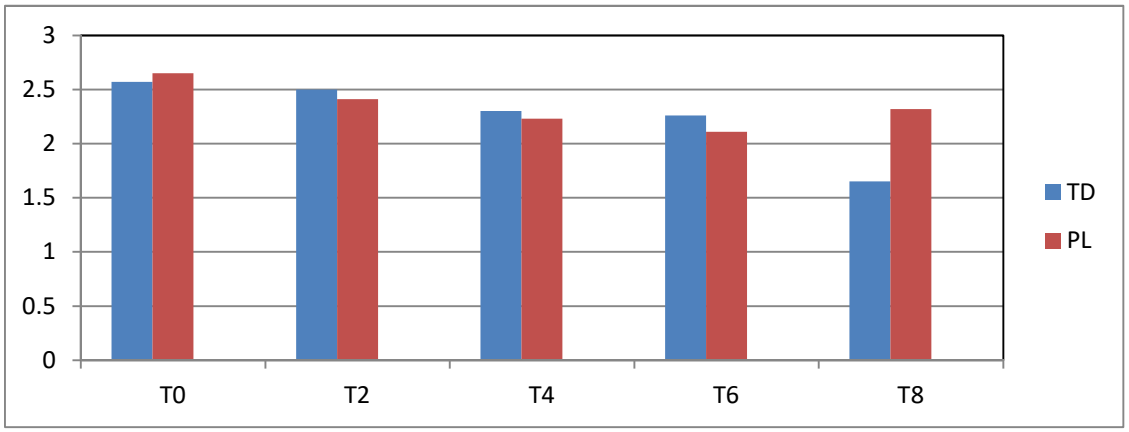


TD: Test drug PL: Placebo

Table 1.2 showing effect of Test drug (Herbokam plus) and Placebo on Epworth sleepiness scale

Epworth sleepiness scale						
Visit		T0	T2	T4	T6	T8
Mean	Test drug	2.57	2.5	2.3	2.26	1.65
	Placebo	2.65	2.41	2.23	2.11	2.32
SD	Test drug	0.86	0.80	0.78	1.15	0.99
	Placebo	0.78	0.8	0.88	0.98	0.88
SE	Test drug	0.064	0.060	0.058	0.086	0.074
	Placebo	0.05	0.056	0.054	0.077	0.065
P- value	Test drug		>0.05 (NS)	>0.05 (NS)	<0.05 (*)	<0.001 (***)
	Placebo		NS	NS	NS	NS

Graph 1.2 showing effect of Test drug (Herbokam plus) and Placebo on Epworth sleepiness scale

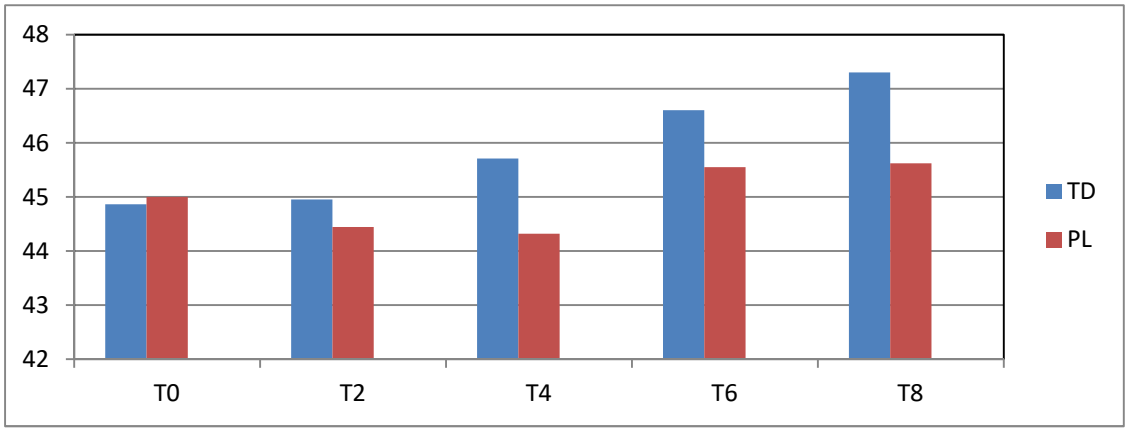


TD: Test drug PL: Placebo

Table 1.3 showing effect of Test drug (Herbokam plus) and Placebo on MOS sleep scale

MOS sleep scale						
Visit		T0	T2	T4	T6	T8
Mean	Test drug	44.86	44.95	45.71	46.6	47.3
	Placebo	45	44.44	44.32	45.55	45.62
SD	Test drug	2.35	3.16	2.93	4.03	5.02
	Placebo	2.33	2.65	2.62	3.66	3.22
SE	Test drug	0.17	0.23	0.21	0.30	0.37
	Placebo	0.11	0.25	0.20	0.28	0.28
P- value	Test drug		>0.05 (NS)	>0.05 (NS)	<0.001 (***)	<0.001 (***)
	Placebo		NS	NS	NS	NS

Graph: 1.3 showing effect of Test drug (Herbokam plus) and Placebo on MOS sleep scale



TD: Test drug PL: Placebo

DISCUSSION

Insomnia could be perpetuated by several physiological and psychological factors such as stressful events, the hyper-arousal of the central nervous system, age-related weakening of sleep homeostasis, and anxious-ruminative personality [6]. The observed reduction in sleep duration is marked in developed countries where people report sleeping for 2h less than was the case a century ago. Several researches have showed that the increased prevalence of hypertension could be associated with sleep deprivation and insomnia. It was proposed that the pathological and physiological mechanisms underlying the relationship between stress-induced insomnia and increased blood pressure are associated with the inappropriate arousal of the physiological mechanisms resulting from an alteration of stress system functions. Sleep plays an important role in homeostatic functions including the suppression of stress system functions, while insomnia is related to the arousal of the central nervous system [7]. According to recent studies, sleep restriction or loss coupled with a worsening quality of sleep as observed in stress-induced insomnia irrespective of the origin could act as a physiological or neurobiological stressor. The alteration of sleep quality could

impair one's adaptation to stress by contributing to the allostatic load that increases blood pressure and compromises stress resilience [8].

Herbokam plus has a proved effect of its ingredients on stress and allied symptoms. ASHWAGANDHA (*Withania somnifera*) directly opposes the reaction of the stress by reducing the amount of Cortisol released by the adrenal glands of the body. Long term production of Cortisol has adverse effect on our health. The main function of Ashwagandha is that it delays the release of cortisol by the adrenals. This prevent the negative effects long term cortisol production on the body and prevents the adrenals from becoming exhausted, a direct antistress effect has been reported by many researchers. [9] BRAHMI (*Bacopa monnieri*) is a plant with apparent anti-anxiety and anti-fatigue effects attributed to its bacosides A and B. Brahmi is a unique nervine tonic, which supports healthy brain functioning, promotes relaxation of mind and concentration. Brahmi is also a potent antioxidant. Antioxidant protection has been linked to improved brain and nervous system function. It is considered one of the best rejuvenatives for the brain, strengthening the nerves and brain cells. [10,11] JATAMANSI (*Nardostachys jatamansi*) is effective to calm the mind. Jatamansi is useful in nervous agitation, tension, headaches, insomnia, restlessness, and mental instability and neurological. Sedative properties help to fight daily life stress and promote healthy sleep patterns. Rationality of the combination is decided by the pilot study experiences of doctors and minimum dose required for significant results as per typical ayurvedic textual references.

Significant results after 4th week during the course of treatment indicates that Herbokam plus capsules need several weeks to act significantly on symptoms of insomnia but results after 6th and 8th week proves consistency of effect. Hence Herbokam plus capsule doesn't act as capsules just to induce sleep in acute conditions but to reduce and calm the stress in holistic manner by adapting to the stress and related insomnia.

CONCLUSION

It is clear from above findings that HERBOKAM PLUS capsules are effective in INSOMNIA. From the above findings it can be concluded that HERBOKAM PLUS capsules can effectively work on insomnia even in 2 and 4 week of treatment but to get highly significant results it should be given for at least 6 to 8 week as statistically highly significant results were observed after 6 and 8 week of treatment.

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