Manasamitra Vataka and *Shirodhara* treatments preserve slow wave sleep and promote sleep continuity in patients with generalized anxiety disorder and co-morbid generalized social phobia

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This study demonstrates the clinical efficacy of *Manasamitra Vataka* and *Shirodhara* (Ayurvedic treatments) over clonazepam in preserving slow wave sleep and promoting sleep quality in patients of generalized anxiety disorder (GAD) with co-morbid generalized social phobia. Whole night polysomnography was carried out to assess the sleep architecture and spindle–delta dynamics. The study highlights the sleep promoting and preserving nature of *Manasamitra Vataka* and *Shirodhara* in GAD patients with co-morbid generalized social phobia. Ayurvedic treatments were helpful in improving the subjective quality of sleep and preserve sleep organization. Further studies are needed to confirm the potential of Ayurvedic interventions as a treatment of choice in the management of anxiety disorders.

Keywords: Clonazepam, generalized anxiety disorder, *Manasamitra Vataka*, *Shirodhara*, sleep architecture.

Introduction

GENERALIZED anxiety disorder (GAD) is a common disabling chronic disorder characterized by excessive worry accompanied with a wide range of physical symptoms like sweating, palpitation, etc. Social phobia (SP) is one of the most frequent co-morbidity of GAD, characterized by irrational fear of public humiliation or embarrassment.

Sleep disturbances are common manifestation of major depressive and anxiety disorders[1,2]. Relatively little research has been focused on sleep disturbances in anxiety disorders compared to affective disorders. Disturbances in sleep such as trouble in falling asleep or staying asleep, increased daytime fatigue, decreased sleep efficiency, increased sleep latencies, intermittent awakenings, reduced slow wave sleep (SWS) and rapid eye movement (REM) sleep states have been reported in patients with GAD[1,3,4]. Though sleep disturbances are reported in patients with social phobias, polysomnographic studies to ascertain the sleep architecture among GAD patients with co-morbid social phobia are scanty. Additionally, conventional anxiolytic agents such as clonazepam have been reported to affect sleep quality. Short-term use of benzodiazepines helps improve the sleep quality, sleep duration and efficiency, but alters the sleep architecture[5]. Long-term treatment has many deleterious effects on sleep[6]. Serotonin–norepinephrine reuptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI) on the other hand, suppress REM sleep and increase nocturnal arousals[7]. Considering such side effects of these agents on sleep, newer treatment strategies are encouraged in the management of anxiety disorders. An alternative system of medicine such as Ayurveda is one such possibility and anxiety was found to be the strongest predictor (odds ratio 3 : 1; 95% confidence interval, 1.6–6.0) for patients to use this system of medicine[8]. *Manasamitra Vataka*[9] and *Shirodhara* therapy (dripping of medicated oil over the forehead) are the most widely used Ayurvedic treatments for GAD. We have demonstrated the clinical effectiveness of *Manasamitra Vataka* and *Shirodhara* therapy over clonazepam in the management of GAD with co-morbid generalized social phobia, as these treatments were found to have potent anxiolytic properties[10]. The present study investigates the effectiveness of these treatments on sleep organization in GAD patients with co-morbid generalized social phobia.

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Methodology

This was an open label, randomized, controlled, parallel-group study. Patients attending the psychiatry outpatient department of psychiatry at the National Institute for Mental Health and Neurosciences (NIMHANS), Bengaluru were recruited for the study. The methodology used is described in a previous publication[10]; however, important components are described here.

Patients

Right-handed patients ($n = 72$), between 20 and 55 years of age, diagnosed with GAD and co-morbid generalized social phobia according to the DSM-IV-TR criteria by a psychiatrist and meeting Hamilton anxiety rating scale (HARS) >18 (ref. 11), were recruited from the psychiatric outpatient department at NIMHANS. Patients with significant depression (Beck depression inventory scores >17), any other AXIS I and medical disorders, or on any psychotropic drugs within four weeks prior to the study were excluded. Patients with substance abuse, as well as pregnant and lactating females were excluded. Patients were explained about the nature and design of the study and informed consent was obtained. The study was initiated after obtaining approval from the Institute ethics committee.

Treatment

Patients were randomized (blocked randomization) into one of the three groups; Group-I, ($n = 24$) received tablet *Manasamitra Vataka* (100 mg, twice daily, for 30 days according to the literature)[9], group-II ($n = 24$) received *Shirodhara*[10] with *Brahmi tailam* (oil-based extract of *Bacopa monniera*) in the morning[12] for the first seven days in addition to tablet *Manasamitra Vataka* as mentioned for group-I. *Manasamitra Vataka* is classical drug[9]; details of its compound formulation has been provided in the earlier study[10]. *Manasamitra Vataka* tablets were procured from the Central Research Institute (Ayurveda), Cheruthuruthy, a unit of the Central Council for Research in Ayurvedic Sciences, Department of AYUSH, Ministry of Health and Family Welfare, Government of India. Group-III ($n = 24$) received clonazepam tablet (0.25 mg in the morning and 0.50 mg at night) for 30 days. Medications were administered in the morning and 1 h prior to the habitual sleep time.

Whole night polysomnography and sleep architecture assessment

Subjects were asked to maintain a sleep diary and abstain from alcohol, caffeine and naps two weeks prior to the study until completion of the treatment. In addition, whole-night polysomnographic (PSG) recordings were made in a semi-sound proof recording chamber (sleep cabin) under video-monitored supervision in a standard sleep laboratory setting during the patients' habitual sleep timings. We carried out whole-night PSG for two consecutive nights, both before as well as following the treatment intervention. In both cases, the first night's recording was for habituation to the laboratory settings and the second night's recording was for sleep architecture assessments. PSG was recorded according to the method described by the Rechtshaffen and Kales[13].

EEG was recorded using disc electrodes placed bilaterally in frontal (F3, F4), central (CZ), and occipital (O1, O2) positions based on the 10–20 system recording of EEG introduced by Jasper[14]. EOG electrodes were placed on both canthi and EMG was recorded from the chin muscles. EEG and EOG were recorded with a time constant of 0.3 sec and a sensitivity of 5 μV/mm and low pass filter 70 Hz, whereas EMG had a time constant of 1.0 sec and sensitivity of 5 μV/mm and low pass filter 70 Hz respectively, using a 32-channel digital Neurofax EEG instrument (Neurofax EEG 2110, Nihon Kohden, Japan). The electrical impedance was kept below 3 KΩ. The monopolar derivation of EEG and EOG was utilized for assessment of the sleep stages using Polysmith software (version 1.7.8R16H; Nihon Kohden, Japan). Epoch by epoch visual scoring was done manually by a trained scorer blind to the study. Sleep architecture and assessment of sleep variables such as sleep efficiency, sleep onset latency, total sleep time, duration of each sleep stages, etc. have been assessed according to Rechtshaffen and Kales classification of sleep stages[13].

Assessment of spindle–delta dynamics

A sub-sample of the PSG data acquired from group-I and group-III patients (group-I: $n = 9$; group-III: $n = 10$; age-matched; data taken both before and after treatment) were subjected to spindle–delta dynamics analysis. First, the EEG data were converted to 'EDF' format (European Data Format; using EDF browser v1.54 software) and imported into EEGLAB toolbox within MATLAB software, where further analysis was carried out. The sleep EEG data were pre-processed using FIR-based band-pass filtering (0.5–35 Hz) and notch filter (50 Hz). Two time–frequency analysis strategies were undertaken on Cz channel of the pre-processed sleep EEG data; a conventional time–frequency approach based on 'Hilbert transform' and another approach based on 'Neuroloopgain' (Polyman v1.15.3 software). Cz channel (referenced to averaged ear lobe electrodes) was chosen as it is a recommended site to observe both spindle and delta oscillations[13].

For the Hilbert transform approach[15], the channel data were first band-pass filtered to 11–16 Hz (for sleep

spindles) or 0.5–4 Hz (for delta waves), and then Hilbert transform applied to extract the instantaneous magnitude (amplitude). The amplitude time series was then squared and further smoothened (using 0.01 Hz low-pass FIR filtering) to represent the spindle or delta dynamics across the whole night.

Neuroloopgain analysis was done using the Neuroloopgain plugin of Polyman software. Neuroloopgain is a measure of micro-continuity of sleep-related delta and spindle oscillations, and is independent of the amplitude of EEG rhythms[16]. In brief, Neuroloopgain or micro-continuity analysis uses a resonance filter (which enhances the frequency band that needs to be passed) to constantly track the rhythmic EEG component (spindle or delta oscillation) between consecutive EEG samples. The filter's response is used to predict the rhythm that is expected to continue to the next (20 ms later) EEG sample, and the fraction of predicted signal that repeats is expressed as micro-continuity percentage (0–100) per second of sleep EEG data. This measure relies on the physiological model that gain in sleep neural network modulates the gain in spindle or delta oscillatory feedback loops.

We used median power, cumulative power (integrated over whole sleep), median Neuroloopgain and cumulative Neuroloopgain (integrated over whole sleep) as measures of spindle–delta dynamics across whole-night sleep data, irrespective of sleep stages. Cumulative parameters were computed as sum of power or Neuroloopgain values above the median value for each subject.

Statistical methods

Statistical analysis was carried out using SPSS version 15.0. Homogeneity of data across the groups was evaluated by χ^2 test. Comparison of groups across different time points was done using repeated measures ANOVA with Bonferroni post-hoc test. Values are reported as mean ± 1 standard deviation (SD). All tests were considered statistically significant $P < 0.05$. By considering the 16 variables of polysomnography, adjustment to multiple corrections was done. $P < 0.003$ was considered to be significant. All the time–frequency measures for sleep spindles and delta waves were log-transformed before statistical analysis using the non-parametric Wilcoxon-signed rank test with significance set at $P < 0.006$ (after Bonferroni's correction for eight measurements per group).

Results

Patient profile

Out of 72 patients recruited for the study, seven (two each from group-I and group-II, and three from group-III) dropped out due to personal problems unrelated to the study. Some patients (two patients each from group-I and group II) reported with mild abdominal colic which subsided without any intervention and six patients from group-III reported daytime sleepiness during the first week of meditation without affecting their daytime functioning. The mean age, gender, height, weight, body mass index, duration, severity of illness and history of sleep disturbances were comparable in all the three groups[10] (Table 1). Baseline values of sleep architecture (Table 2) were also comparable between groups.

Sleep quality assessment

Details of sleep quality (especially time of waking, time of getting out of bed, waking up refreshed or tired, time of going to bed, time of falling asleep, number of night awakenings, duration of night awakenings and factors affecting sleep) were obtained from the sleep diary maintained by the patients. Table 1 provides the sleep disturbances ascertained from the sleep diary. All the interventions brought significant improvement in sleep quality. Effect of interventions was comparable between groups, except the duration of night awakenings ($P = 0.005$), which was improved in group-II ($P = 0.005$) and group-III ($P = 0.006$) compared to group-I (Table 3).

Sleep architecture assessment

Most of the sleep variables such as sleep efficiency index, sleep duration, REM duration, sleep onset latency, REM onset latency, total wake duration, micro arousal index and sleep cycle were comparable between groups (Table 2). The non-rapid eye movement (NREM) state [expressed as % (F (1, 62) = 38.063, $P < 0.001$) and in minutes (F (1, 62) = 32.088, $P < 0.001$)] showed significant changes among groups with time as within group factor; however group-III showed significant reduction compared to group-I (Table 2; Figures 1 and 2).

NREM stage 2 (%)

Repeated measure ANOVA with time as within subject factor and groups as between subject factor showed a significant effect of time (F(1, 62) = 24.994, $P < 0.001$). There was also a significant effect of group (F(2, 62) = 11.857, $P < 0.001$). Post-hoc tests revealed significant increase in group-III compared to group-I ($P = 0.016$) and group-II ($P < 0.001$) after treatment. Group × time interaction was significant (F(2, 62) = 20.972, $P < 0.001$). Post-hoc analysis showed that post-treatment NREM stage (S2) (%) in group-III was significantly increased compared to group-I and group-II ($P < 0.001$; Table 2 and Figures 1 and 2).

Table 1. Patient profile

Clinical profile		Group-I (n = 24)	Group-II (n = 24)	Group-III (n = 24)	P-value
Age (years)		27.46 ± 4.45	26.84 ± 5.02	30.25 ± 6.90	0.126
Gender	Male	20	21	18	0.518
	Female	4	3	6	
Height (cm)		166.97 ± 5.95	166.84 ± 5.71	165.38 ± 8.78	0.674
Weight (kg)		62.59 ± 9.07	61.08 ± 10.34	63.46 ± 12.46	0.730
Body mass index		22.43 ± 2.84	21.91 ± 3.35	23.22 ± 4.23	0.435
Severity of anxiety	Moderate	0	0	1	2.03
	Severe	24	24	23	
Hamilton anxiety rating scale		31.58 ± 3.23	32.63 ± 3.31	31.85 ± 4.28	0.732
Becks anxiety inventory		26.50 ± 5.13	30.63 ± 5.32	26.57 ± 7.92	0.055
Becks depression inventory		13.66 ± 4.70	14.41 ± 2.31	12.52 ± 3.74	0.286
Epworth sleepiness scale		6.22 ± 3.43	6.35 ± 4.10	6.28 ± 5.26	0.968
Duration of illness (years)		6.44 ± 4.87	7.35 ± 3.75	7.48 ± 6.33	0.735
Age of onset (years)		21.01 ± 5.71	19.49 ± 6.08	23.76 ± 6.86	0.102
H/O sleep disturbance	Yes	12	14	13	0.336
	No	12	10	11	
Total patients recruited		24	24	24	
Drop-outs		2	2	3	0.316
Completed study		22	22	21	

Data expressed as mean and standard deviation.

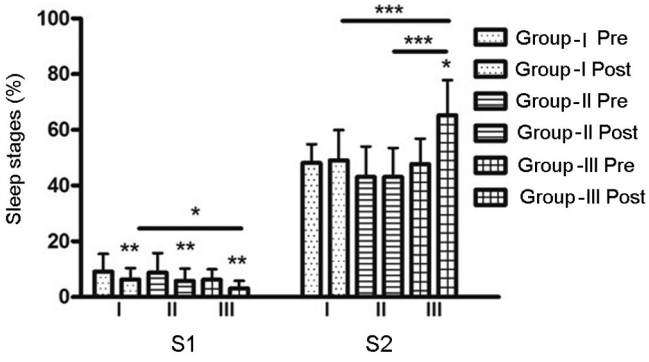

Figure 1. Changes in non-rapid eye movement (NREM) sleep stages S1 and S2 in group-I (n = 22), group-II (n = 22) and group-III (n = 21) assessment pre- and post-intervention. Results are expressed as mean ± standard deviation (SD). Level of significance is $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

NREM slow wave sleep

Repeated measure ANOVA with time as within subject factor and groups as between subject factor showed a significant effect of time ($F(1,62) = 17.710$, $P < 0.001$). There was also a significant effect of group ($F(2,62) = 6.368$, $P = 0.003$). Post-hoc tests showed significant decrease in group-III compared to group-I ($P = 0.004$) and group-II ($P = 0.020$). Group × time interaction was significant ($F(2,62) = 31.138$, $P < 0.001$). Post-hoc analysis showed that post-treatment SWS in group-III was significantly decreased compared to group-I and group-II ($P < 0.001$; Table 2 and Figures 2 and 3).

Major significant changes were observed in NREM S2% and for SWS between groups. Post-treatment increase in NREM S2% ($P < 0.001$) and decrease in SWS ($P < 0.001$) was observed in group-III compared to group-II and group-I. The REM sleep states were not altered in patients and remained the same following treatment in all three groups. The representative hypnograms (Figure 2) highlight the changes brought about by the interventions.

Spindle–delta dynamics across the whole night

Group I showed no significant difference in any of the spindle or delta dynamics parameters between pre- and post-treatment (Table 4 and Figure 4). Whereas group-III showed significant reduction in median ($P = 0.004$) and cumulative ($P = 0.002$) Neuroloopgain values of spindle, and median ($P = 0.002$) and cumulative ($P = 0.002$) power values of delta (Figure 5), indicative of reduced spindle and delta genesis during SWS.

Discussion

This study comprehensively evaluated the distinct changes in sleep architecture brought about by *Manasamitra Vataka* with or without *Shirodhara* and clonazepam interventions in GAD patients with co-morbid generalized social phobia. Ayurvedic treatments were found to be more effective in promoting and preserving SWS thus maintaining the normal sleep architecture, whereas clonazepam treatment grossly altered the sleep architecture in GAD patients.

Insomnia is quite prevalent in GAD[17] and almost 60–70% patients with GAD reported sleep disturbances such as trouble falling and staying asleep, increased daytime fatigue, irritability and difficulty in coping[1,3]. Patients with SP reported poor sleep quality, longer sleep latency,

Table 2. Comparison of sleep architecture variables in three groups of patients before and after the interventions

Sleep variables	Intervention	Group-I (n = 22)	Group-II (n = 22)	Group-III (n = 21)	P value (comparison between groups)		
					I–II	I–III	II–III
Sleep efficacy index (%)	Before	89.87 ± 7.11	90.62 ± 6.23	88.97 ± 6.86	1	1	1
	After	89.06 ± 8.04	92.26 ± 5.42	91.69 ± 5.02	0.294	0.534	1
Sleep duration	Before	413.68 ± 57.23	416.79 ± 49.94	392.35 ± 41.14	1	0.501	0.343
	After	400.53 ± 60.23	422.61 ± 35.72	415.76 ± 38.79	0.357	0.857	1
NREM stage-1 (%)	Before	9.11 ± 6.46	8.76 ± 7.02	6.18 ± 3.75	1	0.337	0.482
	After	6.29 ± 4.08	5.77 ± 4.45	3.15 ± 2.66	1	0.027*	0.085
	P value	0.001**	0.001**	0.001**	–		
NREM stage-2 (%)	Before	48.16 ± 6.72	43.10 ± 10.97	47.68 ± 9.18	0.211	1	0.315
	After	49.08 ± 10.85	43.14 ± 10.36	65.21 ± 12.69	0.260	<0.001***	<0.001***
NREM SWS (%)	Before	18.77 ± 6.06	18.27 ± 7.61	18.29 ± 8.52	1	1	1
	After	20.46 ± 6.79	18.57 ± 7.13	7.21 ± 7.57	1	<0.001***	<0.001***
REM (%)	Before	23.96 ± 4.88	29.85 ± 6.94	27.85 ± 7.79	0.014*	0.177	0.983
	After	24.15 ± 7.62	30.18 ± 8.28	24.41 ± 7.29	0.037*	1	0.053
Wake (min)	Before	46.43 ± 33.09	42.97 ± 32.80	49.59 ± 33.41	1	1	1
	After	49.09 ± 34.19	36.77 ± 27.32	37.95 ± 23.66	0.483	0.629	1
NREM stage-1 (min)	Before	37.90 ± 25.66	36.02 ± 27.46	24.95 ± 16.44	1	0.237	0.397
	After	25.86 ± 17.15	24.47 ± 18.67	13.28 ± 11.62	1	0.04*	0.08
	P value	0.001**	0.002**	0.002**	–		
NREM stage-2 (min)	Before	197.36 ± 32.76	179.09 ± 47.53	186.04 ± 35.51	0.381	1	1
	After	195.09 ± 40.88	171.38 ± 61.66	256.26 ± 73.61	0.585	0.004**	<0.001***
NREM stage-3 (min)	Before	46.47 ± 18.22	41.18 ± 15.68	46.67 ± 17.16	0.921	1	0.885
	After	45.18 ± 17.71	41.90 ± 19.59	20.50 ± 19.30	1	<0.001***	0.001***
NREM stage-4 (min)	Before	31.77 ± 24.40	34.54 ± 29.28	36.30 ± 61.91	1	1	1
	After	36.86 ± 23.95	40.65 ± 31.22	9.40 ± 18.52	1	0.002**	<0.001***
REM (min)	Before	100.84 ± 29.65	125.97 ± 38.27	110.57 ± 38.77	0.069	1	0.489
	After	94.14 ± 40.58	126.86 ± 38.61	101.47 ± 30.70	0.014*	1	0.084
SOL (min)	Before	10.15 ± 7.61	10.09 ± 8.03	11.09 ± 8.28	1	1	1
	After	10.00 ± 6.78	9.09 ± 12.78	8.97 ± 8.04	1	1	1
ROL (min)	Before	93.36 ± 32.99	97.34 ± 53.85	91.76 ± 37.59	1	1	1
	After	105.63 ± 43.08	99.27 ± 41.97	127.00 ± 75.25	1	0.629	0.315
Micro arousal index	Before	15.14 ± 6.51	12.89 ± 4.16	13.94 ± 6.35	0.601	1	1
	After	15.36 ± 7.33	12.17 ± 5.60	11.94 ± 4.82	0.251	0.202	1
Sleep cycle	Before	4.18 ± 1.05	4.36 ± 0.95	4.38 ± 1.11	1	1	1
	After	3.72 ± 1.03	4.04 ± 0.89	4.00 ± 1.18	0.945	1	1

Data expressed as mean ± SD. *P < 0.05, **P < 0.01, ***P < 0.001. NREM, Non-rapid eye movement sleep; REM, Rapid eye movement sleep, SOL, Sleep onset latency; ROL, REM onset latency; SWS, Slow wave sleep.

frequent awakenings and daytime dysfunctions[18]. In the present study, almost 56% of patients reported history of disturbed sleep, delayed period of sleep onset, more awakenings per night and non-refreshing type of sleep. Following treatment interventions, patients from all groups reported improvement in sleep quality and felt refreshed after sleep. Sleep architecture profiles revealed that the major sleep variables like sleep efficiency, duration, micro-arousals, etc. were almost within the normal physiological limits[19]. Some studies however revealed inconclusive reports; either increase or decrease in NREM S1, NREM S2, NREM S4, changes in NREM S3 and REM sleep, etc[4]. Differences observed in both subjective and objective sleep assessments could be associated with sleep disturbances in the patients. The SWS states are restorative in nature and Ayurvedic interventions preserved them. Additionally, Ayurvedic treatments (*Manasamitra Vataka* treatment with and without *Shirodhara*) reduced the NREM S1 sleep, thus reducing sleep onset latency, reduced intermittent awakenings, and helped maintain sleep continuity. Clonazepam treatment enhanced NREM S2, REM (%), REM onset latency but significantly reduced SWS, which is an important component of restoration. Benzodiazepine[20] has been shown to grossly alter

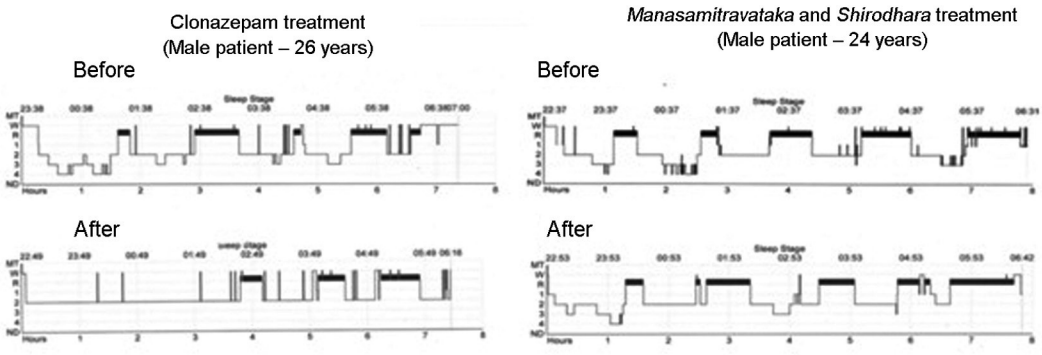

Figure 2. Representative hypnograms of generalized anxiety disorder patients with comorbid generalized social phobia, before and after intervention.

Table 3. Comparison of qualitative sleep parameters from sleep diary in three groups of patients before and after the interventions

Intervention	Group-I (n = 22)	Group-II (n = 21)	Group-III (n = 21)	*P*-value			
				Comparison between groups			
				I–II–III	I–II	I–III	II–III
Wake up refreshed							
Pre	12	9	8	0.367			
Post	16	15	15				
Wake up tired							
Pre	10	13	13	0.138			
Post	6	7	6				
Duration of sleep onset (min)							
Pre	11.36 ± 4.41	11.36 ± 4.92	13.09 ± 5.11	0.599			
Post	8.40 ± 3.89	6.81 ± 2.46	7.14 ± 2.53				
P-value	0.001**	<0.001***	<0.001***				
Number of night awakenings							
Pre	2.18 ± 1.43	2.54 ± 1.18	2.80 ± 1.36	0.545			
Post	1.36 ± 1.09	1.40 ± 0.59	1.42 ± 1.20				
P-value	0.001**	<0.001***	<0.001***				
Duration of night awakenings (min)							
Pre	3.36 ± 1.52	2.63 ± 1.52	2.57 ± 1.43				
Post	2.77 ± 1.30	1.81 ± 0.90	1.80 ± 0.51	0.015	0.005**	0.006**	1
P-value	0.032*	0.003**	0.007**				
Number of days of stress affecting sleep in a week							
Pre	3.09 ± 0.92	2.86 ± 0.88	3.04 ± 0.86	0.919			
Post	1.50 ± 0.51	1.59 ± 0.50	1.42 ± 0.50				
P-value	<0.001***	<0.001***	<0.001***				
Time of getting out of bed (min)							
Pre	9.18 ± 6.31	9.63 ± 4.68	9.52 ± 3.84	0.828			
Post	7.72 ± 4.34	8.04 ± 2.71	6.66 ± 2.88				
P-value	0.046*	0.029*	<0.001***				

Data expressed in mean ± standard deviation.*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

the sleep architecture[5]. Our study also demonstrated such non-restorative quality of sleep by clonazepam. The literature on the effects of clonazepam on sleep architecture is scanty and the present study contributes towards its role on sleep architecture.

Manasamitra Vataka is a compound formulation, which has nootropic, psychotropic and anxiolytic properties[9,10]. Ingredients such as *Withania somnifera* have GABA-mimetic activity[21]; *Bacopa monneira* has been shown to promote sleep[22]. Up-regulation of serotonin receptors[23] and GABAergic modulation of *B. monniera*[24] and *Centella asiatica*[25] have also been reported. However, the effect of external use of *Brahmi* oil (*B. monnieri*) has not been reported. *Shirodhara* treatment has been shown

Table 4. Comparison of sleep spindle–delta dynamics variables in a subsample of group-I and group-III patients before and after the interventions

Group	Sleep spindle–delta dynamics variables	Pre-treatment			Post-treatment			Statistical analysis
		Mean	SD	N	Mean	SD	N	*P*-value
I	Neuroloopgain–delta	51.27	9.34	9	50.10	10.91	9	0.734
	Cumulative Neuroloopgain–delta	716,000.00	170,000.00	9	669,000.00	148,000.00	9	0.426
	Neuroloopgain–spindle	38.29	14.35	9	33.54	11.20	9	0.164
	Cumulative Neuroloopgain–spindle	521,000.00	187,000.00	9	448,000.00	150,000.00	9	0.250
	Hilbert transform–delta	3,800.00	4,180.00	9	7430.00	12,500.00	9	0.250
	Cumulative Hilbert transform–delta	5,360,000.00	6,110,000.00	9	9,560,000.00	16,000,000.00	9	0.164
	Hilbert transform–spindle	52.57	27.72	9	87.03	99.89	9	0.570
	Cumulative Hilbert transform–spindle	72,300.00	43,300.00	9	112,000.00	127,000.00	9	0.359
III	Neuroloopgain–delta	43.77	12.69	10	25.28	14.48	10	0.019
	Cumulative Neuroloopgain–delta	576,000.00	180,000.00	10	338,000.00	198,000.00	10	0.037
	Neuroloopgain–spindle*	35.79	16.32	10	50.37	12.61	10	0.004*
	Cumulative Neuroloopgain–spindle*	478,000.00	221,000.00	10	681,000.00	189,000.00	10	0.002*
	Hilbert transform–delta*	1,560.00	1,710.00	10	587.23	217.18	10	0.002*
	Cumulative Hilbert transform–delta*	2,000,000.00	2,110,000.00	10	770,000.00	280,000.00	10	0.002*
	Hilbert transform–spindle	100.01	76.81	10	77.94	31.33	10	0.160
	Cumulative Hilbert transform–spindle	128,000.00	96,400.00	10	102,000.00	41,900.00	10	0.232

Statistical analysis was done using Wilcoxon signed rank test with a significance threshold set at $P < 0.006$. Hilbert transform-based parameters are represented in μV^2 and Neuroloopgain based parameters in percentage.

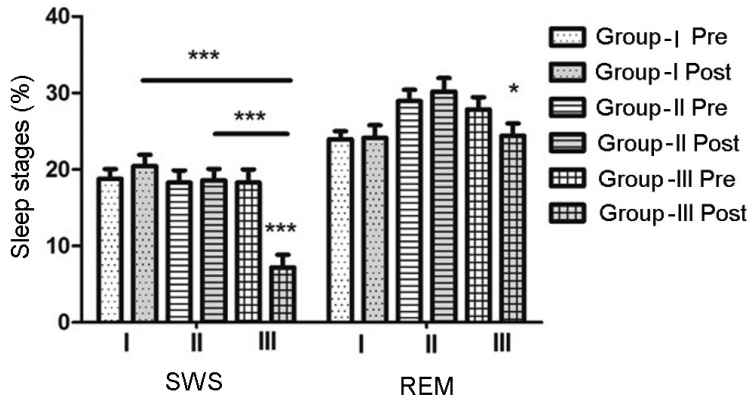

Figure 3. Changes in NREM slow wave sleep (SWS) and rapid eye movement stages of sleep (REM) in group-I ($n = 22$), group-II ($n = 22$) and group-III ($n = 21$) assessment pre- and post-intervention. Results are expressed as mean ± SD. Level of significance is $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

to produce anxiolytic effects as assessed by state-trait anxiety inventory[26–29] and *Shirodhara* effect could be through brain-targeted transcranial drug delivery[30,31]. The present study shows that *Shirodhara* with *Brahmi* oil considerably reduces the micro-arousals and helps in sleep continuity. We have earlier reported about the sleep-promoting effects of *Shirodhara*, as the treatment significantly reduces daytime sleepiness[10]. Moreover, the spindle–delta dynamics examined on a subgroup of patients, also showed no significant alteration after Ayurvedic treatment. On the contrary, clonazepam treatment resulted in deficits in delta power and spindle density (inferred from Neuroloopgain analysis), which are indications of reduced sleep intensity.

Ayurvedic treatments are thus more effective compared to clonazepam in maintaining a proper sleep architecture, spindle–delta dynamics, and also help in preserving SWS. Sleep spindles are believed to be a key player in sleep maintenance, particularly in the progression to deeper SWS and transition to REM sleep. SWS has a significant role in maintaining body homeostasis like cerebral restoration and recovery[32,33]. SWS is the main time period for secretion of anabolic growth hormone[34], for tissue repair and growth[35], synaptic density[36], learning and synaptic plasticity, memory consolidation, especially declarative memory[37] and is involved in the maintenance and consolidation of sleep[38].

The present study has several limitations as it is open-labelled and not a double-blind randomized control study. An additional placebo group would have helped demonstrate the subsequent changes in sleep after the interventions; but this had other ethical implications. Similarly,

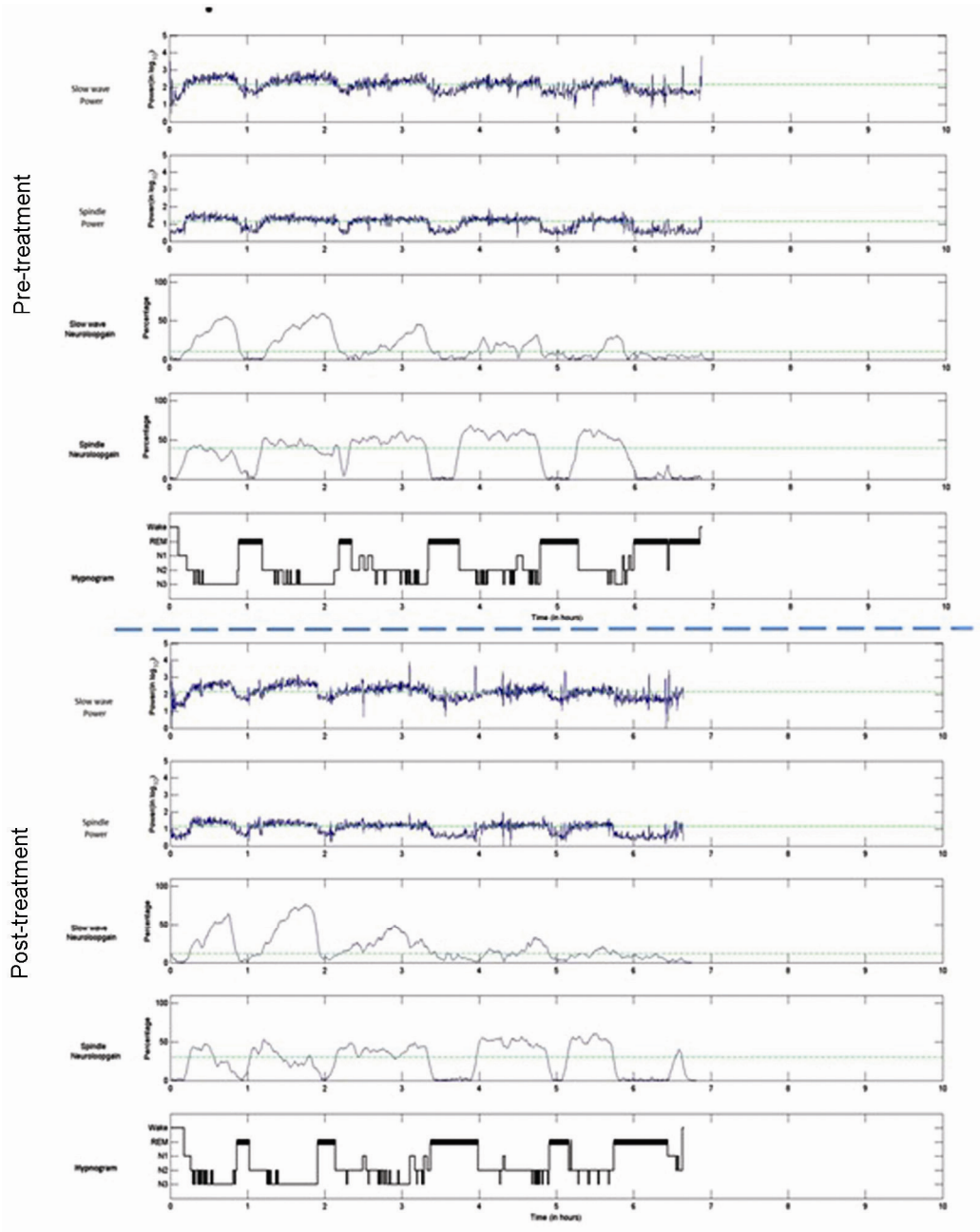

Figure 4. Representative spindle–delta dynamics from group-I (treatment with *Manasamitra Vataka*) before and after intervention.

long-term interventions would have been more effective on the clinical and sleep profiles. As both *Manasamitra Vataka* and *Shirodhara* are being studied for the first time on a psychiatric population[10], further studies are required to understand the profile of the medications on other biological parameters as well.

Overall, the study highlights the sleep promoting and preserving nature of *Manasamitra Vataka* and *Shirodhara* in GAD patients with co-morbid generalized SP. Ayurvedic treatments helped in improve the subjective quality of sleep and preserve sleep organization. They were also found to be highly effective over clonazepam in terms of preserving SWS and maintaining sleep quality. *Shirodhara* treatment had an add-on effect on *Manasamitra Vataka* treatment, as it helped improve the sleep continuity by reducing the micro-arousals and also the daytime sleepiness[10]. Clinical variables outcome showed that Ayurvedic interventions were effective in ameliorating GAD with co-morbid generalized SP and were comparable to clonazepam[10]. Hence Ayurvedic interventions like *Manasamitra Vataka* can be the drug of choice in the comprehensive management of GAD with generalized

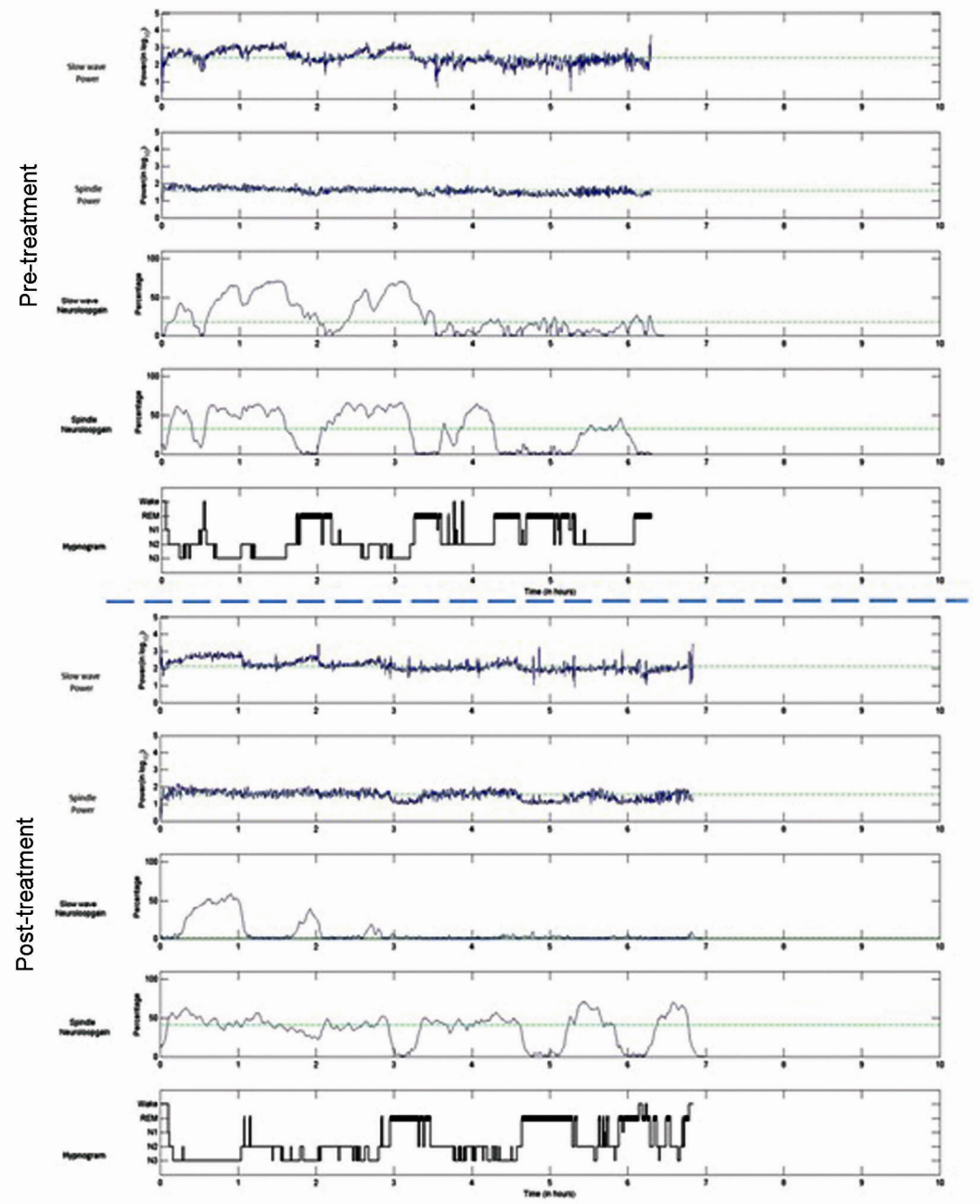

Figure 5. Representative spindle–delta dynamics from group-III (treatment with clonazepam) before and after intervention.

SP. The medications used in the present study are suggestive of an effective comprehensive treatment strategy in GAD with generalized SP.

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