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Melatonin Release and Polysomnographic Architecture in Patients with Mild to Moderate Depression

Jyothi I[1], Ilango K[1], Satish Kumar RC[1], Vasanth K[1] and Dubey GP[2*]

[1]*Interdisciplinary Institute of Indian System of Medicine (IIISM), SRM University, Kattankulathur, Tamil Nadu, India*

[2]*National Facility for Tribal and Herbal Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India*

[*]**Corresponding author:** Dubey GP, National Facility for Tribal and Herbal Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, Tel: 08939012223; E-mail: gpdubey13@gmail.com

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Abstract

Objectives: The association of serum melatonin levels with polysomnographic sleep parameters were investigated in mild to moderate depressed patients.

Methods: Seventy patients with mild to moderate depression (mean age 49.43 ± 6.70) were selected in the study. All patients underwent two successive overnight polysomnography recordings. Venous blood samples were obtained from the patients of two groups at 21:00 h and 6:00 h before and after performing polysomnography. Serum was separated and kept at -80°C. The serum melatonin levels were analysed using microplate reader.

Results: Early morning release of melatonin was significantly correlated with sleep latency (P=0.0026, r=0.4630), [CI=0.3249 to 1.426], sleep efficiency (P=0.049, r=0.3123), [CI=0.01253 to 0.3180] and total sleep time (P=0.006, r=0.516), [CI=0.04966 to 0.1664] when compared to night time release.

Conclusions: Our results showed melatonin in mild to moderate depressed patients, not only found lower night-time levels of serum melatonin, but also found a phase shift in depressed patients.

Keywords: Polysomnography; Melatonin; Sleep efficiency; Sleep latency; Depression

Introduction

The gold standard method for the diagnosis of sleep disorder is polysomnography (PSG), which is a study that is performed throughout the night in a laboratory [1]. However, other diagnostic methods can be used for the investigation of sleep disorders and subjective and objective assessments of sleep parameters may differ due to sleep misperception and measurement effects. While subjective estimates may be biased by a person's own sleep perception, objective assessment method (such as PSGs), may be considered distressing, thus changing the quality and quantity of a person's usual sleep. Exposure to PSG equipment, e.g., head and chest sensors or sleeping in an unfamiliar setting such as a laboratory, may interfere with the person's habitual sleep pattern [2,3]. Melatonin (5-methoxy N-acetyl tryptamine) is a neurohormone secreted primarily by the pineal gland under the control of the master circadian clock, the suprachiasmatic nucleus (SCN) [4]. The pineal gland produces melatonin from L-tryptophan amino acid, which is secreted into the circulation and cerebrospinal fluid (CSF) circulation. Abnormal functioning of this gland gives rise to psychiatric disorders [5].

Several studies suggest a role for melatonin influencing the timing of sleep onset and sleep duration [6-8]. In humans, melatonin administration during the subjective daytime promotes sleep by inducing earlier sleep onset and generating longer sleep duration [9-11]. Daily melatonin ingestion can entrain free running circadian rhythms in blind individuals [12,13] and pharmacological suppression of nocturnal melatonin secretion increases total wake time and concomitantly decreases both non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep [14].

Depressed patients experience difficulty falling asleep, difficulty staying asleep and early morning awakenings. Analysis of slow wave sleep (SWS) in non-rapid eye movement (NREM) sleep has shown that delta wave counts in patients with depressive disorders are decreased when compared to healthy controls. Fast frequency beta and elevated alpha activities have been recorded during sleep in depressed patients, indicating that hyperarousal and increased sleep fragmentation are major characteristics of sleep in depression. These changes are present in non-medicated patients or in clinical remission, suggesting that they are trait-like features of depressive illness [15]. To date there is no published scientific reports on the correlation of polysomnographic sleep parameters with the melatonin release in mild to moderate depressed patients. Hence the study has been designed to study the polysomnography architecture and to evaluate the relationship with melatonin release in patients with mild to moderate depression.

Subjects and Methods

Study design

A cross-sectional study was carried out between January 2013 and March 2014. The study was performed in accordance with the current revision of the Declaration of Helsinki and was approved by the Human Ethic Committee of SRM Medical College Hospital and Research Centre, SRM University. Written informed consent was

obtained from the patients, their family, or an authorized representative.

Sample size

For documentation and justification of results, the sample size is the most important factor to be estimated. There is no published literature available from India to determine the relationship between polysomnographic parameters and melatonin release in mild to moderate depressed patients, therefore with 95% confidence level and 20% bound on error of estimation, a sample of 58 subjects was required using assumed sample and population correlation coefficient 0.7 and 0.8 respectively. Adding a further 10% for non-response subjects, a final sample size of 70 study participants was calculated. A sample size of at least 58 was estimated, using a significance level of 0.05, and a power of 80%. Therefore, a minimum sample of 70 adult subjects was targeted to cover the study objectives.

The following formula was used for sample size calculation

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2}{\left[FZ(\rho_1) - FZ(\rho_0)\right]^2} + 3$$

$$FZ(\rho_1) = \frac{1}{2}\ln\left[\frac{1+\rho_1}{1-\rho_1}\right]$$

$$FZ(\rho_0) = \frac{1}{2}\ln\left[\frac{1+\rho_0}{1-\rho_0}\right]$$

Where, ρ_0=Population correlation coefficient, ρ_1=Sample correlation coefficient, $Z_{1-\frac{\alpha}{2}}$= Desired confidence level, $1-\beta = Power$

Study population

Patients were recruited from inpatients and outpatient services for the evaluation and treatment of depression in SRM Medical College Hospital and Research Centre, SRM University. All the subjects were 35 yrs of age or above and gave informed consent. Based on the inclusion criteria, 70 patients were recruited who met DSM-V criteria on the structural clinical interview. Patients were excluded from the study if they had severe depressive symptoms or grief reaction in the previous 6 months. Patients with any clinically important medical disease or abnormality on physical examination, such as recent head trauma or other brain injuries, thyroid abnormality, acute heart disease, as well as other Axis I psychiatric disorders or cognitive disturbance were also excluded.

Polysomnography parameters

All patients underwent two successive overnight polysomnography recordings. Because the patients were in unfamiliar surroundings and the study criteria required them to sleep more naturally, the first recording session was necessary to make the patients familiar with their surroundings. Overnight polysomnography was conducted using standard techniques and all procedures were performed in accordance with guidelines published by the American Academy of Sleep Medicine (AASM). Polysomnography contained continuous recordings of central and occipital electroencephalograms, bilateral electro-oculograms, submental and bilateral tibial electromyograms and electrocardiogram. Nasal and oral airflow were measured using both thermocouple sensors and pressure transducer airflow (PTAF) monitoring devices.

Body positioning was verified by infrared video recording. Studies were scheduled to last between 6 h and 8 h and were terminated following the final wakening. Polysomnograms were scored in 30-sec epochs, following criteria of Rechtschaffen and Kales for sleep staging (Rechtschaffen and Kales, 1968). All parameters were recorded by a trained polysomnography technician. In addition, all investigations were reviewed and interpreted by a neuro specialist from SRM Medical College Hospital and Research. A number of sleep variables were derived from the sleep-stage score data. Total time in bed (TIB) was computed as the total time from lights-out to wake-up time. Total sleep period (TSP) was defined as the length of time from sleep onset to wake up.

Estimation of melatonin

Venous blood samples (5 ml) were obtained from the patients at 21:00 h and 6:00 h before and after performing polysomnography. The blood samples were centrifuged (5430R, Eppendorf) and serum was separated in 30 min. Separated serum was kept at -80°C. Serum melatonin levels were analysed by microplate reader (thermo scientific multiscan) using human melatonin (MLT) ELISA kit (Cat. No: E01M0005).

Statistical analysis

All the variables were presented as mean ± standard deviation. Statistical analysis was carried out using GraphPad Prism version 6.0 and MS-Excel 2013. Pearson correlation co-efficient was calculated to see the correlation between polysomnographic parameters and serum melatonin levels. For all statistical analyses a P value<0.05 was considered statistically significant.

Results

Demographic parameters

Demographic details like level of activity, educational status, and socio-economic class are shown in Table 1. Among the 70 patients analysed, 41.42% of males and 58.58% of females in the age range of 49.43 ± 6.70. 70.8% of the subjects were married and 29.2% were unmarried and 65% of the respondents described their relationship with their partners as good, while 35% described their relationship as poor. 52.85% patients were active in their working environment. In total, 25.71% of patients were graduated and 54.28% were in upper middle socio-economic status (Table 1).

PSG sleep parameters were correlated with the night and early morning release of melatonin (Figure 1), cumulative total sleep time was 355.5 ± 49.3 min, WASO (59.95 ± 13.07 min), N1 (246.7 ± 80.4 min), N2 (38.7 ± 10.0 min), N3 (42.8 ± 16.1 min), N-R (9.32 ± 7.23 min), early morning melatonin (56.31 ± 11.24 pg/ml) and night time release of melatonin (30.45 ± 9.45 pg/ml). Results were indicated; early morning release of melatonin was significantly increased when compared to the night time melatonin release with the consideration of PSG parameters.

Demographic details	Patients (n=70)
Age in years (Mean ± SD)	49.43 ± 6.70
Male, n (%)	29 (41.42)
Female, n (%)	41 (58.58)
Level of activity, n (%)	
Active	37 (52.85)
Routine work	27 (38.57)
Passive	6 (8.57)
Educational status, n (%)	
Post Graduate/Graduate	18 (25.71)
Intermediate/Diploma	9 (12.85)
School	40 (57.14)
Illiterate	3 (4.28)
Socioeconomic class, n (%)	
Upper	-
Upper middle	38 (54.28)
Lower middle	26 (37.14)
Lower	6 (8.57)

Table 1: Demographic details of patients with mild to moderate depression.

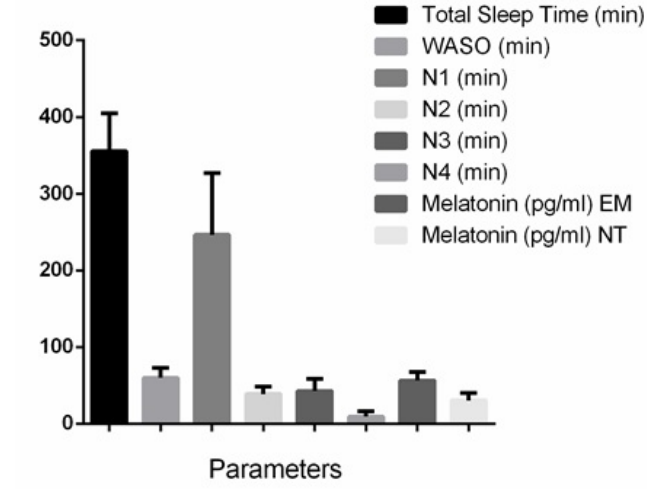

Figure 1: Polysomnographic sleep parameters compared with melatonin release (early morning and night).

Association between sleep latency and melatonin early morning, night time release was shown in Figures 2 and 3. Early morning release of melatonin was significantly correlated with sleep latency (P=0.0026, r=0.4630), [CI=0.3249 to 1.426] but night time release was not correlated with sleep latency (P=0.250, r=0.0345), [CI=-0.3628 to 1.348]. Similar that sleep efficiency was well correlated with early morning release of melatonin (P=0.049, r=0.3123), [CI=0.01253 to 0.3180] not with the night time release (P=0.263, r=0.204), [CI=-0.05773 to 0.2585] (Figures 4 and 5).

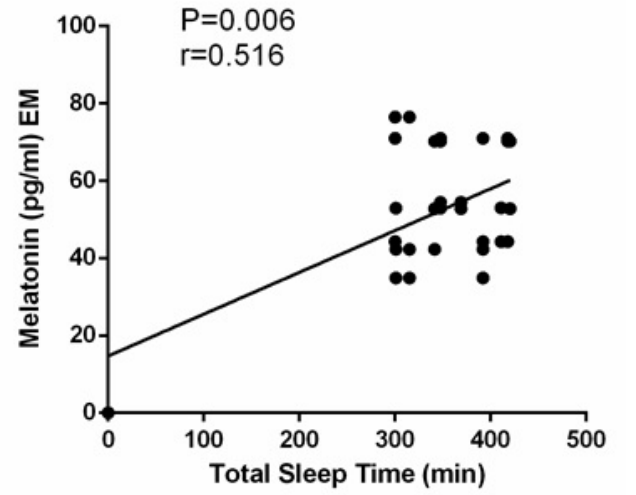

Figure 2: Total sleep time in association with early morning melatonin release in mild to moderate depressed patients.

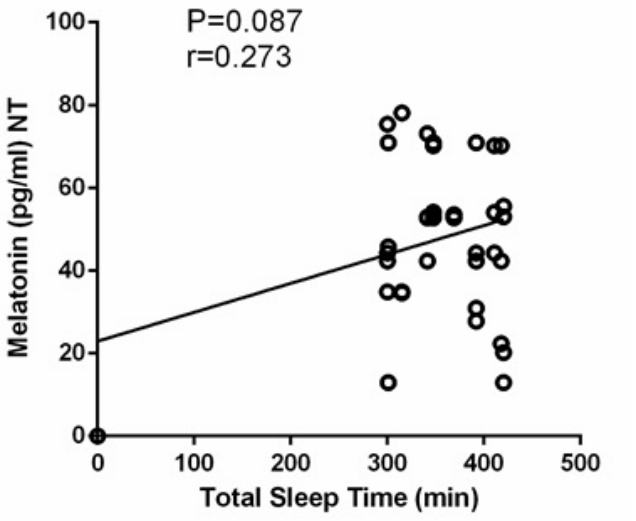

Figure 3: Correlation of total sleep time with night melatonin release in mild to moderate depressed patients.

Total sleep time was related graphically with early morning and night time release of melatonin, early morning melatonin release was well correlated with total sleep time (P=0.006, r=0.516), [CI=0.04966 to 0.1664] but night time melatonin release was not significant with total sleep time (P=0.087,r=0.273), [CI=-0.01087 to 0.1508] (Figures 6 and 7).

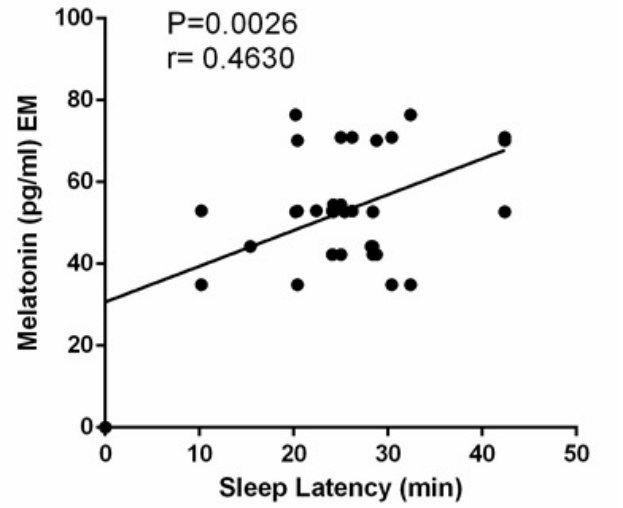

Figure 4: Association between sleep latency and early morning melatonin in mild to moderate depressed patients.

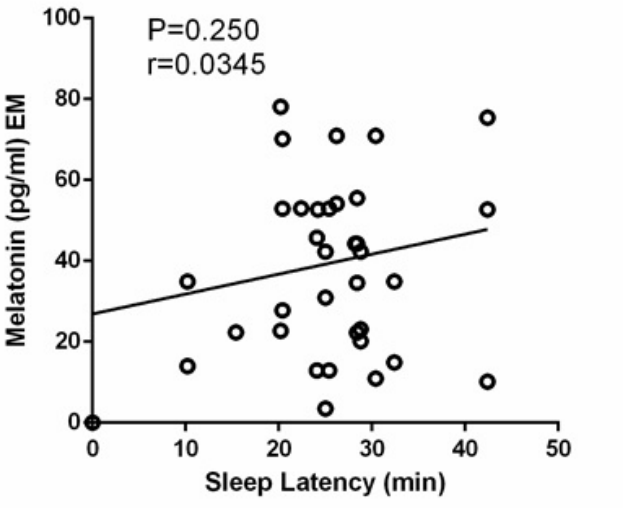

Figure 5: Correlation between sleep latency and night melatonin release in mild to moderate depressed patients.

Discussion

The current study was undertaken to evaluate the polysomnographic sleep parameters in patient with mild to moderate depression and to correlate the sleep parameters with night and early morning melatonin release. In polysomnographic findings, slow-wave activity (SWA) seen on the electroencephalogram (EEG) during non-REM sleep is a marker of the homeostatic drive to sleep; thus, the amount of SWA is greatest in the first sleep cycle when sleep propensity is high and gradually reduces in subsequent cycles as sleep debt is made up and sleep drive diminished. The total amount of SWS is often decreased in mild to moderate depression. This reduction may be related to condensed regional cerebral blood flow seen in the orbito frontal and anterior cingulate cortex during slow-wave sleep (SWS) in imaging studies [16] and it may be a consequence of the abnormalities in this area described in depression [17].

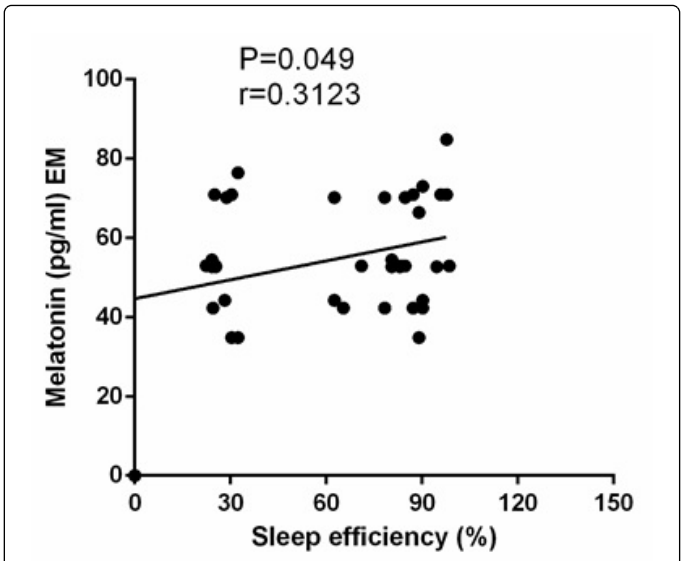

Figure 6: Sleep efficiency in association with early morning melatonin release in mild to moderation depressed patients.

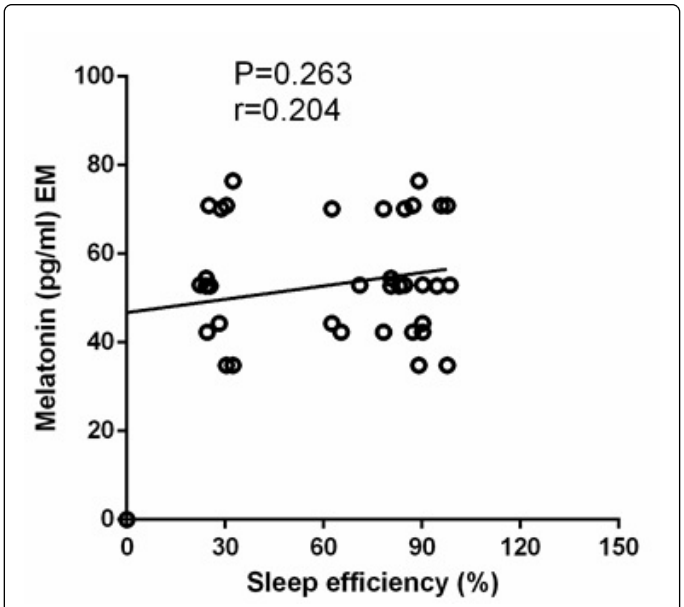

Figure 7: Sleep efficiency in correlation with night melatonin release in mild to moderation depressed patients.

The decline of both melatonin secretion and sleep efficiency with age are thought to be related phenomena. Mild to moderate depressed patients and elderly insomnias are reported to exhibit lower melatonin production than those good sleepers of the same age. The most common disturbances documented in visually scored polysomnograms are: decreased sleep efficiency (a composite measure that takes into account difficulty falling asleep, nocturnal awakenings

and early-morning awakening), decreased slow-wave sleep (which reflects decreased stage III and stage IV sleep time), reduced REM latency and increased REM intensity (which is typically expressed as increased REM density, a ratio of a measure of REM intensity divided by time spent in REM sleep) [18,19].

Longitudinal studies of sleep disturbance in depression indicate that some features do not fully normalize following recovery. The most state-independent or persistently abnormal disturbances are decreased slow-wave sleep and reduced REM latency, which show some degree of heritability. SWS are often decreased in depression, especially in the first sleep cycle, with a relative increase of SWS in the second sleep cycle [20]. A close relation has been reported between decreased total SWS and recurrence of depression. Hatzinger and others showed that diminished SWS persisted in the study group who subsequently had a recurrence of depression [21]. Our results are consistent with some previous studies that showed lower night-time levels of melatonin in depressed patients [22], not only found lower night-time levels of serum melatonin in depressed patients, but also found a phase shift in depressed patients.

Conclusion

In conclusion, the present study revealed that early morning serum melatonin levels were associated with sleep efficiency, sleep latency and total sleep time. The release of melatonin was phase shifted in mild to moderate depression.

Conflict of Interest

The authors have declared no conflict of interests.

Acknowledgment

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