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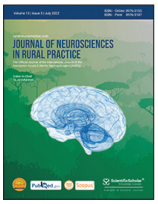

Brief Report

Correlation between levodopa equivalent daily dose (LEDD) and sleep quality in Parkinson's disease patient as weighed by Parkinson's disease sleep scale-2 (PDSS-2)

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ABSTRACT

Parkinson's disease (PD) is the most prevalent movement disorder that affects the central nervous system. The main non-motor symptoms of PD are sleep disturbances. One reason for sleep impairments in PD is the impact of dopaminergic medications. Given the variability in each patient's medication regimen, a standardized measure like levodopa equivalent daily dose (LEDD) is used. The purpose of this observational cross-sectional analytical study is to determine the association between LEDD and sleep quality in PD patients, as weighed by the PD sleep scale-2. There are 50 participants in the walk-in patient and inpatient wards in Dr. Soetomo General Academic Hospital and Airlangga University Hospital Surabaya. Spearman analysis showed a non-significant result ($P = 0.15$). Bivariate analysis of anxiety against sleep quality revealed a significant relationship ($P = 0.017$). After performing a stratified analysis, there is no correlation ($P = 0.863$) in the non-anxiety group.

Keywords: Levodopa equivalent daily dose, Parkinson's disease sleep scale-2, Parkinson's disease, Sleep quality

INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, following Alzheimer's dementia, affecting the central nervous system and signified by the loss of dopaminergic neurons in the substantia nigra.[1,2] The main symptoms of PD consist of akinesia, rigidity, and resting tremor while non-motor symptoms often consist of sleep disturbances, olfactory dysfunction, constipation, and cognitive behavioral disorders.[1,3]

In 2016, there were 6.1 million PD cases worldwide, showing a 2.4-fold increment from 2.5 million cases in the 1990s. It continues to rise and is estimated to reach 8.7 million cases worldwide in 2030 because the elderly population is expected to increase. In Indonesia, the latest data showed approximately 876.665 sufferers out of 238.452.952 total population in 2018. Hence, attention to the impact of this disease has become increasingly important.[3] Notably, sleep disturbances are a significant issue, with a prevalence of 45–90% among PD patients. The factors contributing to sleep disturbances are multifactorial, including the influence of dopaminergic medications.[4-6]

MATERIALS AND METHODS

Study design

This cross-sectional, hospital-based, observational study was conducted in the Department of Neurology in Surabaya, Indonesia.

Study subjects

Fifty PD patients (30 males and 20 females) were recruited from Dr. Soetomo Academic General Hospital and Airlangga University Hospital in Surabaya, Indonesia. PD was diagnosed using the UK PD Society Brain Bank criteria. Inclusion criteria were PD patients in Hoehn and Yahr stages I–IV on levodopa therapy for at least one year. Exclusion criteria included major neurocognitive and psychiatric disorders, recent drug modifications, and conditions affecting sleep. The study was conducted from February to July 2024, and written informed consent was obtained. The study was approved by the institutional ethics committee and followed international ethical guidelines.

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Ethical compliance statement

The authors declare that they have reviewed the Journal's stance on ethical publication and confirm that this work adheres to those guidelines.

Data collection

Sociodemographic and clinical data were collected from all participants, including age, gender, education level, occupation, ethnicity, Hoehn and Yahr stage, Montreal cognitive assessment-Indonesia (MoCA-INA) score, co-morbid anxiety and depression, sleep quality, and levodopa equivalent daily dose (LEDD) value. Total LEDD was calculated using an updated equation. Sleep quality was assessed using the PD sleep scale-2 (PDSS-2) questionnaire, where a score ≥ 15 indicates poor sleeper and 0–14 indicates good sleeper. Depression and anxiety were evaluated using hospital anxiety and depression scale-Indonesia (HADS-INA), excluding severe cases. Anxiety/depression severity was categorized as 0–7 (none), 8–10 (mild), 11–15 (moderate), and 16–21 (severe). Severe cases were excluded due to their potential impact on sleep quality.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences V26.0 and Microsoft Excel. Normality was tested with the Shapiro–Wilk test, and normally distributed variables were expressed as mean ± standard deviation, while non-normally distributed variables were presented as median and range. Categorical data were shown as frequencies and percentages. Spearman's correlation test was used for variable relationships, and bivariate Chi-square analysis was performed. A $P < 0.05$ was considered statistically significant.

RESULTS

Demographic characteristics

The study included 50 participants, with 30 males (60%) and 20 females (40%). Age-wise, 29 participants (58%) were under 60 years, while 21 (42%) were aged 60 or older, with an average age of 63.08 ± 12.45 years. The demographic data for education, occupation, and ethnicity varied.

Clinical characteristics

The data provided presents an overview of clinical assessments in a group of participants with PD. According to the Hoehn and Yahr staging, 16% of the participants are in Stage I, 36% are in Stage II, 40% are in Stage III, and 8% are in Stage IV. The MoCA-INA score has a median score of 27, with a range between 25 and 30. The HADS-Anxiety score has a mean score of 5.84 ± 3.01, while the HADS-Depression score has a median score of 4.5, ranging from 0 to 13. The LEDD has a median of 422.5, with a range of 37.5–1166.67. Finally, the PDSS-2 score has a median score of 13.5 (ranging from 2 to 42), with 26 participants identified as good sleepers and 24 as bad sleepers.

Anti-Parkinsonian drug profile

There were 90% of the participants (45 subjects) on multi-therapy, while 10% (5 subjects) were on single therapy. Levodopa was the most common medication (94%), followed by cathecol-o-methyl-transferase (COMT)-inhibitors (58%), non-ergot dopamine agonists (44%), ergot dopamine agonists (2%), and trihexyphenidyl (52%).

Correlation analysis

Spearman's test showed no significant correlation between LEDD and PDSS-2 score ($P = 0.15$, r = 0.21). Chi-square analysis revealed that the HADS-Anxiety score significantly affected sleep quality ($P = 0.017$, odds ratio = 6.49, CI 1.53–27.56) and after stratifying by anxiety, Spearman's test again showed no significant correlation between LEDD and PDSS-2 score ($P = 0.863$, r = 0.03) [Table 1].

DISCUSSION

This study focuses on exploring the correlation between LEDD and sleep quality in PD patients. It was found that sleep quality can be influenced by various factors, including the effects of dopaminergic treatment. The study by Chang *et al*. (2019) indicated that patients with poor sleep quality tend to have a longer disease duration, more advanced disease stage, and higher levels of depression and anxiety. This research also noted that although a correlation was expected between disease severity (measured by the Unified Parkinson's Disease Rating Scale) and sleep quality, the results were not significant ($P = 0.65$). This aligns with findings from Young *et al*. (2002), which showed that sleep disturbances could occur in the initial phases of the disease.[7]

High LEDD may contribute to sleep disturbances in PD patients through multiple mechanisms. First, levodopa stimulates D1 dopamine receptors, which can induce wakefulness. However, in Parkinson's patients, the number of D1 receptors is reduced, leading to excessive stimulation and poor sleep quality when high doses of levodopa are administered. In addition, levodopa affects melatonin levels, a hormone critical for sleep

Table 1: Correlation of LEDD and PDSS-2 score.

Variable	Correlation coefficient (r)	*P*-value
LEDD and PDSS-2 score*	0.21	0.15
LEDD and PDSS-2 score in non-anxiety group*	0.03	0.863

*Spearman's test, LEDD: Levodopa equivalent daily dose, PDSS-2: Parkinson's disease sleep scale-2

regulation. While higher LEDD levels can increase melatonin, Parkinson's patients already have significantly lower melatonin levels compared to the general population. As a result, high LEDD doses mainly exacerbate receptor activation rather than improving melatonin production.[8,9]

Our study has several limitations that should be considered. First, we did not assess the timing of medication administration before sleep, which could have influenced sleep quality, especially if medications were taken too close to bedtime. In addition, when comparing LEDD dosages, our study found a median LEDD of 422.5, which is lower than the mean LEDD of 617.06 ± 454.73 reported by Chang *et al*. This suggests that the higher medication doses in their study may have had a more pronounced impact on sleep quality. Finally, our study had a smaller sample size of 50 participants, while Chang *et al*. included 134 participants. This difference in sample size resulted in insufficient statistical power for our analysis, and based on an r = 0.21, we would have needed approximately 172 participants to achieve adequate statistical power.[5]

This study has several strengths, such as the ability to compare different types and cumulative doses of anti-Parkinson medications on sleep quality, the use of LEDD, which is not commonly used in clinical practice, and the implementation of the PDSS-2 questionnaire, which is easy and quick for PD patients to complete.

CONCLUSION

There was no correlation found between LEDD and sleep quality in PD patients, as assessed using the PDSS-2 questionnaire, which means that a cutoff value for LEDD could not be determined. To enhance the study, several recommendations could be considered. First, employing a prospective cohort design that follows participants for a month after medication administration would allow for the observation of changes in sleep quality over time. Second, incorporating quantitative plasma levodopa levels as a parameter alongside the LEDD would provide a more precise comparison of the medication's impact on sleep. Third, excluding patients who take levodopa <4 h before sleep could minimize potential biases related to the timing of medication administration, which may affect sleep quality. Fourth, analyzing the PDSS-2 questionnaire by breaking down the subgroups for each sleep disturbance component would offer a more detailed understanding of specific sleep issues. Finally, using more objective measurement tools, such as polysomnography or actigraphy, would enable a comprehensive assessment of sleep quality and architecture, thus reducing subjective bias associated with self-reported PDSS-2 responses.

Ethical approval: The research/study was approved by the Institutional Review Board at Komite Etik Penelitian Kesehatan RSUD Dr. Soetomo Surabaya, number 0917/KEPK/II/2024, dated February 7, 2024.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

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