

The Association between Melatonin Administration and Sleep Quality in Acute Ischemic Stroke Patients

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Abstract

Objective : To assess the association of Melatonin administration during an acute phase of ischemic stroke patients towards sleep quality

Design : This study used a randomized control trial design

Setting : Subjects participated from three different hospitals in Medan, North Sumatra; Haji Adam Malik General Hospital Medan, Universitas Sumatera Utara General Hospital Medan and RS Tk.II Putri Hijau Medan.

Patients and participants : 32 acute ischemic stroke patients

Interventions : Eligible subjects divided into 2 main groups with simple random sampling method. First group consisted of 16 subjects who received Melatonin 10 mg, once daily for 30 days and second group consisted of 16 subjects received placebo tablet, once daily for 30 days. No major adverse effect was reported during observation.

Measurements and results : Sleep quality were measured by The Pittsburgh Sleep Quality Index (PSQI) questionnaire at day 1 of admission and at day 30 of the study when subjects returned for routine checkup at Neurology clinic or via telephone for each subject. PSQI global score ≤ 5 indicates good sleep quality while global score > 5 indicates a poor sleep quality. Subjects were mainly male (56,3%), mean age of $59,6 \pm 10,8$ years and having Batak ethnicity (37,5%). Measurement at day 1 indicated poor sleep quality on both group with PSQI global score $7,9 \pm 2,0$. Upon completion group who received Melatonin 10 mg once daily marked an improvement in PSQI global score from mean score of $7,8 \pm 1,7$ at day 1 to mean score of $5,1 \pm 2,4$ at day 30. No remarkable improvement from Placebo group with similar mean score before and after protocol ($8,0 \pm 2,4$ at day 1 vs $6,9 \pm 3,1$ at day 30).

Conclusions : There is an association between melatonin administration and sleep quality of acute ischemic stroke patients.

Introduction

Stroke is a condition when the blood supply of the brain is disrupted either by blockage or ruptured vessels resulting in focal or global neurological deficit which lasted >24 hours or ended with death, globally affecting more than 100 million people with 77 million of them were ischemic strokes in 2019.^{1,2} Ischemic stroke is the one which its disruption caused by atherosclerosis, cardioembolism or inflammatory mechanism that occlude brain vessel thus required fine management especially in acute phase.³ The first hours to months can be classified to an acute phase by several classification; Hyperacute in the first to 24 hours after clinical manifestation appeared, acute within the 1-7 days, early Subacute from the first week-3 months and late subacute within 3-6 months post attack.⁴ The hyperacute and acute phase is critical for neural plasticity mechanism in which this phases will be very decisive for patients outcome therefore comprehensive management including factors that affecting the mechanism should be observed and maintained. One of many factors affecting neural plasticity according to several studies is sleep quality during the acute phase of the stroke, in which a poor sleep quality

will impaired the recovery process and overall outcomes.⁵⁻⁷ To measure patient's sleep quality clinician could benefit from The Pittsburgh Sleep Quality Index (PSQI) questionnaire to assess 7 main domain of sleep objectively including subjective overview, sleep latency, sleep duration, habitual efficiency, sleep disorder, usage of sleep medication and daytime dysfunction within a month with good validity and reliability test results. The questionnaire nature as an interview made it easily applicable on daily practice and can also be performed via telemedicine. A global score of PSQI with value ≤ 5 indicates a good sleep quality within a month while global score > 5 indicates otherwise.⁸⁻¹²

Post stroke sleep disorders increasingly an issue amongst post stroke patients, accounts for upto 78% of all cases.¹³⁻¹⁵ Symptoms including breathing difficulty while sleeping, insomnia, hypersomnia, parasomnia and impaired circadian rhythm within 1-6 months post stroke.¹³ Most ischemic stroke patients study reported insomnia post attack, which affecting overall sleep quality and outcomes.¹⁴⁻¹⁶ Studies from Khot et al, Sterr et al and Duss et al also reported good sleep is important in recovery phase of ischemic stroke in which they observed less deterioration in group of patients with better sleep quality during care.¹⁴⁻¹⁶ Several study analyzed such outcomes during acute phase of ischemic stroke may be associated to Melatonin, which involved in pathophysiology of ischemic stroke due to its nature as antioxidant and neuroprotectant and its production could also be affected by the ischemic process in brain tissue since it was produced by pineal gland, effectively in night to help initiate sleep process.^{17,18} Experimental study from Andrabi et al, Hao et al, Romero et al and Vinogradov et al regarding administration of melatonin in rats with ischemic stroke condition reported similar results with a lower infarct volume with an observation of upregulation mechanism in neurogenesis and neuroplasticity in MT2 receptor.¹⁸⁻²¹ Andrabi et al reported specifically the role of melatonin in acute phase of ischemic stroke would affect the excitotoxicity process by glutamate, decreased apoptosis by inhibiting Cyt c release, decreased inflammation process by inhibiting Cytokine release and decreased excess of free radicals thus inhibits oxidative stress in which all of those resulted in infarction or cell death.¹⁸ A study from Zhang et al regarding relationship of nocturnal concentrations of Melatonin, Gamma-Aminobutyric Acid (GABA) and total antioxidants in peripheral blood samples of patients with insomnia post stroke reported a lower Melatonin concentrations in ischemic stroke patients (<100 pg/mL) which may be related to insomnia suffered.²² All of these studies indicate that a melatonin level during an acute phase would be essential to determine patient outcomes overall and sleep quality specifically.

The supplementation of Melatonin to manage common sleep difficulties has been observed with common preparations available on the market varied between 1 to 10 mg, to be taken once daily in night time, and relatively safe to use due to its No-Observed Adverse Effect Level (NOAEL) value larger than 200 mg/kg.²³⁻²⁶ In Indonesia the usage of Melatonin has been approved for clinical condition especially sleep disturbance during Coronavirus disease-19 (COVID-19) infection.²⁶ The usage of melatonin in stroke management has not been common, although in several cardiac condition including hypertensive heart disease and post coronary care reported improved sleep quality after administration.^{27,28} One study reported melatonin supplementation during emergency setting may benefits patient with acute ischemic stroke not eligible for reperfusion therapy, with significant decrease in National Institute of Health Stroke Scale (NIHSS) and modified Rankin Score (mRS) observed in day 5, day 30 and day 90 post stroke.²⁹ One study from Vebrian et al also reported Melatonin had positive impact towards sleep quality of perimenopause women with minimal adverse effect.³⁰ For all of these backgrounds the authors therefore interested to assess a relationship between Melatonin administration and sleep quality within acute ischemic stroke patients.

Materials and Methods

This study was performed as a randomized control trial with 32 subjects participated from 3 different hospitals in Medan, North Sumatra; Haji Adam Malik General Hospital Medan, Universitas Sumatera Utara General Hospital and equally divided to 2 main groups with simple random sampling method. Eligible subjects classified as acute ischemic stroke patients admitted and treated within said institution and approved their participation with an informed consent statements. First group consisted of 16 subjects who received Melatonin 10 mg supplementation, taken once daily at night time for 30 days and the second group consisted of 16 subjects who received Placebo tablet, taken once daily at night time for 30 days. The measurement of sleep quality were obtained from PSQI questionnaire at day 1 before intervention and day 30 upon completion when subjects returned to routine checkup at Neurology clinic or interviewed by phone. No major adverse effects were reported during observation and all subjects completed the study protocol.

Results

This study obtained 32 subjects from Haji Adam Malik General Hospital Medan (RSUP HAM; 56,2%), Universitas Sumatera Utara General Hospital Medan (RS USU; 34,4%) and RS Tk.II Putri Hijau Medan (RUMKIT; 9,4%). Subjects were predominantly male (53,1%), with mean age of $59,6 \pm 10,8$ years and 37,5% have a Batak ethnicity. No significant difference within the variation according to p value $> 0,001$ (Table 1).

Table 1. Subject Characteristics

Group	P-value
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	Melatonin-10 mg	Plasebo	
	(n=16)	(n=16)	
Gender			0,228 ^a
Male	17 (53,1%)	10 (62,5%)	7 (43,8%)
Female	15 (46,9%)	6 (37,5%)	9 (56,2%)
Age			0,691 ^b
Mean ± SD	59,6 ± 10,8	60,4 ± 9,9	58,8 ± 11,9
Median (Min-Max)	58 (35-78)	58 (46-77)	58,5 (35-78)
Ethnicity			0,642 ^c
Batak	12 (37,5%)	6 (37,5%)	6 (37,6%)
Javanese	11 (34,4%)	6 (37,5%)	5 (31,2%)
Malay	8 (25,0%)	3 (18,8%)	5 (31,2%)
Minang	1 (3,1%)	1 (6,2%)	0 (0%)
Location			0,897 ^c
RSUP HAM	18 (56,2%)	9 (56,2%)	9 (56,2%)
RS USU	11 (34,4%)	6 (37,5%)	5 (31,2%)
RUMKIT	3 (9,4%)	1 (6,3%)	2 (12,6%)

a: Chi-square test; b: T-independent test; c: Mann-Whitney test

Table 2 listed measurement at day 1 before intervention with most subjects had a poor sleep quality (mean PSQI global score at $7,9 \pm 2,0$). Only 3 subjects (9,4%) had a good sleep quality according to PSQI. Upon completion at day 30 most subjects still had a poor sleep quality overall with mean global score of $6,0 \pm 2,9$ although the improvement in amount of subjects who had a good sleep quality was observed with total of 16 subjects (50%).

Table 2. Collective Measurements of PSQI

PSQI Global Scores	n : 32
Day 1	
Sleep Quality	
Good Sleep (PSQI score ≤ 5)	3 (9,4%)
Poor Sleep (PSQI score > 5)	29 (90,6%)
Day 30	
Sleep Quality	
Good Sleep (PSQI score ≤ 5)	16 (50,0%)
Poor Sleep (PSQI score > 5)	16 (50,0%)

Analysis of the relationship between both group intervention towards PSQI global scores was performed with T-paired independent test. The first group who received Melatonin 10 mg once daily for 30 days marked an improvement in PSQI global score either quantitatively; from only 1 subject (6,2%) who had good sleep quality in day 1 to 10 subjects (62,5%) in day 30 but with no significant relevance due to $p \text{ value} > 0,001$ (Table 3); or from mean value of PSQI global score of $7,8 \pm 1,7$ at day 1 to mean score of $5,1 \pm 2,4$ at day 30 with $p \text{ value} 0,001$. Within Placebo group a similar mean score before and after protocol was observed ($8,0 \pm 2,4$ at day 1 vs $6,9 \pm 3,1$ at day 30). With $p \text{ value} > 0,001$ observed in the Placebo group then the result has no significant value (Table 4).

Table 3. sleep quality differences in quantitative manner

	Kualitas Tidur		P-value
	Baik (Skor PSQI ≤ 5)	Buruk (Skor PSQI > 5)	
Day 1			1,000 ^a
Plasebo	2 (12,5%)	14 (87,5%)	
Melatonin 10 mg	1 (6,2%)	15 (93,8%)	
Day 30			0,157 ^b
Plasebo	6 (37,5%)	10 (62,5%)	
Melatonin 10 mg	10 (62,5%)	6 (37,5%)	

Table 4. Difference of sleep quality before and after intervention within groups

Group	PSQI Global Scores		P-Value^a
	Day 1	Day 30	
Melatonin-10 mg			0,001
Mean ± SD	7,8 ± 1,7	5,1 ± 2,4	
Median (Min-Max)	8 (5-10)	4,5 (3-10)	
Placebo			0,288
Mean ± SD	8,0 ± 2,4	6,9 ± 3,1	
Median (Min-Max)	8 (3-12)	7 (2-12)	
P-Value^b	0,766	0,072	

Discussion

Ischemic stroke is a condition when the blood supply of the brain is disrupted by an occlusion in brain blood vessels resulting in focal or global neurological deficit which lasted >24 hours or ended with death, globally affecting 77 million in 2019, and mostly found in male individual with comorbids and unhealthy lifestyle including smoking and alcoholism.^{1,2} Most subjects were male and having Batak ethnicity may be related to findings from previous studies that male gender were more susceptible to stroke; up to 1.25 times higher than female due to various stroke risk factors often presented in male and also hormonal which estrogen in female may have part in vascular condition; and the fact that this study conducted in North Sumatra.³¹ A study from Tambunan et al reported Batak ethnicity had an increased tendency towards stroke due to their custom of Alcohol consumption. Age is also a stroke risk factor due to aging process involving Advanced Glycation End Products (AGEs) accumulation in which also had a part in elasticity of vascular endothel thus increasing risk of blood supply in the brain.³²

Majority of subjects had poor sleep quality at day 1 relevant to several previous studies that stated most ischemic patients also had poor sleep quality during hospitalization and post stroke due to various factor including insomnia, circadian rhythm sleep disturbance, sleep apnea and hypersomnia. This finding also relevant from previous literature cited that this may be related to the decrease of Melatonin level in circulation (<100 pg/mL) due to the damage in brain tissue caused by ischemic stroke mechanisms thus causing sleep disorder amongst the patient. Improvement of sleep quality according to PSQI global scores and amount of subjects who had good sleep quality at day 30 in Melatonin group is in concordance to previous studies by Andrabi et al, Ferracioli-Oda et al, Sadanandan et al and Mehrpooya et al that Melatonin supplementation is able to be used for the treatment of primary sleep disorders and with sufficient Melatonin level in patient helped with the supplementation would also affects the mechanism of inflammation, cytotoxicity, apoptosis and excess of free radicals that will lower infarction volume / cell death in brain tissue thus lead to an overall better outcome and better sleep quality amongst ischemic stroke patients.^{18,23,29,33} No improvement observed in Placebo group is relevant to systematic review by Ramos et al about Melatonin efficacy in stroke patients that of all experimental studies which implemented placebo would resulted in no significant changes in terms of overall sleep quality.³⁴

The limitation of this study were as follows: that the measurement of Melatonin serum pre- and post- intervention was unavailable, the observation of another factor that would affect the sleep quality e.g sleep hygiene, lighting around bed or depression risk amongst patient and family support post hospitalization due to technical difficulties. Conclusion of this study were as follows : that there is an association between Melatonin administration and sleep quality of acute ischemic stroke patients who received Melatonin 10 mg, once daily for 30 days (p value 0,001), majority of subjects at day 1 had poor sleep quality (n=29; 90,6%; PSQI global score 7,9 ± 2,0) and predominantly male, having a Batak ethnicity (37,5%).

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