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Poor Sleep Quality Increased the Risk of Frequent Episodic Tension-Type Headache on the Medical Students in Udayana University

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Abstract: ***Headache is a pain that is located in orbitomeatal line caused by stimulation of pain structures. Frequent Episodic tension-type headache is a primary headache that often experienced mainly by medical students. The relationship of sleep disorders and headaches have been known since long ago, but the relationship between them is still not known with certainty. This study aims to prove that poor sleep quality increases the risk of frequent episodic tension-type headache on medical students in Udayana University of Bali. This study was conducted at the Udayana University from December 2016 to February 2017 using a case control design of the 62 study subjects. We found 22 subjects (71%) with poor sleep quality in cases groups and 14 subjects(45.25%) in control groups. Statistical analysis showed that a significant relationship between poor sleep quality and frequent episodic tension-type headache with p = 0.039 and OR = 2.968 (95%CI = 1.039-8.749). Poor sleep quality statistically significant to increase the risk of Frequent Episodic tension-type headache, on the medical students in Udayana University of Bali.***

Keywords: Frequent Episodic tension-type headache, poor sleep quality, medical students

1. Introduction

Headache is a pain that is located on the orbitomeatal line caused by stimulation of pain sensitive structures. In general, this headache can be caused by a primary cause or secondary to other diseases. Most of the people in all his life had experienced of headache. Mostly experienced headaches are primary headaches, which tension-type headache is a headache that is found vary often. Recently the incidence of tension-type headache is quite commonly found mainly on the student. The incidence of headache have impact on the quality of life of the student.

The prevalence of headache in students from several studies obtained varied between 33% -98%, whereas in the global adult population prevalence of tension-type headache is 42%. Study conducted on students at the University of Kirkuk, in 2012 found the incidence of headache is more common in women students than men with prevalence of headache is 33.5% on male and 43.4% on female students . Study conducted by Falvagina et al (2010) in Brazil obtained the proportion of students experiencing tension-type headache incidence of 12.8%. Another study conducted by Ghorbani (2013) in Iran against the medical students that the prevalence of tension-type headache was 44.6%, which in this stu\dy was found in the 3rd semester student and 5th semester. Study conducted by Deleu (2001) in Oman found that the prevalence of tension-type headache was 12.2% while 13.9% were male students and 11.1% were women. [1-4]

Study by Mahardika (2015) to the students of the Faculty of Medicine Udayana University obtained the proportion of tension-type headache was 57.5% while the study conducted by Suryawijaya (2015) to the students faculty of medicine Udayana University obtained the proportion of tension-type headache was 60.3% which was not much different than the study conducted by Mahardika. [5,6]

The relationship of sleep disorders and headaches have been known since long ago, but the relationship between them is still not known with certainty. Tension-type headache is a type of headache most commonly found associated with sleep disorders.[7]

Serotonin is the main neurotransmitter that plays a role in the communication between cells. Serotonin is released and received by the brain and spinal cord. If obtained a low serotonin levels then one would be more irritable and aggressive, than that a person will feel pain, headaches, and depression. [8]

Shukla et al (1987) found a decrease in plasma serotonin levels in patients with tension-type headache. Jensen (1994) obtained plasma serotonin levels higher than normal levels in patients with tension-type headache. While study conducted by Leira et al (1993) found that plasma serotonin levels were higher than normal in patients with tension-type headache. Bendsten et al (1997) found that normal serotonin levels in patients with tension-type headache.[9-12]

This study aims to prove that poor sleep quality increases risk factor for Frequent Episodic tension-type headache on medical students in Udayana University of Bali.

2. Subjects and Methods

This study used a case-control design and conducted at Udayana University Bali from December 2016 - February 2017. The subjects are medical students of Udayana university 5th and 6 th semester. The exclusion criteria of this study are students who suffer from headaches other than Frequent Episodic tension-type headache, history of brain

tumor (neoplasm), abnormalities in the cranium, eyes, ears , nose, sinuses, teeth, and mouth, the use of alcohol and drugs.

Criteria for episodic tension-type headache from The International Classification of Headache Disorders, 2nd edition : there were 10 episodes in 1-15 days / month for at least 3 months (12-180 days / month), headache lasts 30 minutes - 7 days , headache has at least two characteristics (location bilateral, pressing / binding (not pulsed), light or moderate, does not become heavy with regular physical activity, and not obtained photophobia, phonophobia, nausea and vomiting, and is not associated with other diseases.[13]

Quality of sleep in this study examined using Pitssburgh Sleep Quality Inventory (PSQI). Poor sleep quality determined when PSQI score <5.[14]

Serum serotonin levels examined using ELISA method wear Serotonin ELISA, IBL International Gmbh Kit Catalog No: RE59121 by Prodia clinical laboratory Denpasar. Prior to sampling, the patient is recommended fasting for 6-8 hours. Patients eat as usual and not consume foods that contain serotonin such as meat, chicken, eggs, milk, fish, avocados, bananas, coffee, pineapple, and tomato 1 day before the examination. Blood samples were taken in the morning around 8-10 in the morning by Prodia officers by 5 ml blood venipuncture and stored in a sealed tube, allowed to stand for 15-30 minutes at room temperature and then centrifuged at 4500 x per minute for 10 minutes to obtain platelet without plasma. This material is stored in a cooler at a temperature of -20℃ before being checked by enzyme immunoassay (EIA), type BA10-0900. With acylation reagent, serotonin experienced quantitative derivatization into N-acylserotonin.[15]

Low serum serotonin levels are determined when serum serotonin levels <101 ng/ml while the normal serum serotonin levels is 101-283 nanograms per millimeter (ng/ml).[16]

Analysis was done using SPSS 20.0 for windows. Bivariate analysis was done using Chi-Square with contunuity correction. The level of significance is expressed by $p < 0.05$ and the odd ratio (OR) with 95% confidence interval (CI). Multivariate analysis with logistic regression method also included to control for other variables that could affect the study results. The study was approved by the Ethic Committee of Udayana University.

3. Result

A total of 62 subjects with frequent episodic tension-type headache with 41.9% was male and 51.8% was female. The median age in both cases and control groups was 20 years. The mean levels of serotonin in the case group was 251.09 ± 89.14 lower than the control group, where the average serotonin levels in the control group was 265.25 ± 125.42. The basic charachteristics of the subjects are displayed in Table 1.

Table 1: Baseline characteristic of study subjects

Variable	Cases N (%)	Control N (%)
Age (Years) median (min-maks)	20 (20-21)	20 (19-21)
Sex Male Female	 13 (41.9%) 18 (58.1%)	 13 (41.9%) 18 (58.1%)
Serotonin level (ng/ml) Mean ± SD	251.09 ± 89.14	265.25 ± 125.42

Total subjects with poor sleep quality were 22 subjects (71.0%) in the cases group and 14 subjects (45.2%) in the control group and there is a significant relationship between poor sleep quality and frequent episodic tension-type headache. Low serotonin serum level only found in 2 subjects (6.5%) both in cases and control groups and there is no significant relationship bertween low serotonin serum level and (Table 2)

Multivaraiate analysis obtained an independent factor that affecting frequent episodic tension-type headache were the pericranial tenderness.

Table 2: Bivariate analysis between factors with frequent episodic tension-type headache

	Cases	Control	OR	
	N (%)	N (%)	(95% CI)	*P*
Sleep Quality Poor Good	 22(71.0%) 9 (29%)	 14(45.2%) 17(54.8%)	 2.968 (1.039-8.479)	 0.039*
Pericranial Tenderness Yes No	 14(45.2%) 17(54.8%)	 5(16.1%) 26(83.9%)	 4.282 (1.303-14.078	 0.013*
Serotonin Level Low Normal	 2(6.5%) 29(93.5%)	 2 (6.5%) 29 (93.5%)	 1.00 (0.132-7.587)	 1.00
Depresion Yes No	 3(9.7%) 28(90.3%)	 0(0%) 31(100%)	 2.107 (1.611-2.756)	 0.238
Anxiety Yes No	 2(6.5%) 29(93.5%)	 0(0%) 31(100%)	 2.069 (1.593-2.688)	 0.492

*Statistically Significant

Table 3: Multivariate Analysis

	Coefisient	OR (95% CI)	P
Pericranial Tenderness	1.521	4.576 (1.286-16.281)	0.019
Constanta	-23.081	0	0.999

*Statistically Significant

4. Discussion

We found 22 subjects (71%) in the cases groups and 14 subjects (45.2%) in control groups with poor sleep quality. Deleu et al in 2001found that 72.4% subjects with sleep disorders have a headache, but in this study Deleu used subjects with either migraine headaches or tension-type headache. Antara (2015) found that 95.65% subjects with poor sleep quality have headache.[17,18]

There is a significant association between poor sleep quality with frequent episodic tension-type headache. In the general population, this sleep disorder associated with any type of headache and severity of headache. Dysregulation of sleep can also trigger tension-type headache. Dysregulation of sleep will lower the threshold of stimulation of headache. The fluctuations in the levels of serotonin and melatonin affects the relationship of sleep and headache. Some studies found that structures such as the dorsal raphe nuclei, locus ceruleus and nucleus suprachiasmatikus that regulate the neurotransmitter play a role in sleep and headache.[19]

In this study, two subjects (6.5%) with low serum serotonin levels found in cases and control groups with average levels of serotonin in the cases group was lower compared with the control group. and found no significant relationship between low serum serotonin levels with frequent episodic tension-type headache. This study is not different from study conducted by Leira et al (1993) where Leira et al say that platelet serotonin levels were higher in subjects with tension-type headache compared with the controls. Study conducted by Jensen and Hindberg in 1994 also found increased levels of serum serotonin in patients with tension-type headache. Bendsten et al 1997 also get a plasma serotonin levels were normal in patients with tension-type headache.[11, 20, 21]

There are several mechanisms of serotonin contribute to tension-type headache. Platelet activation during the headache causes the release of serotonin into plasma. This is also supported by an increase in betatromboglobulin plasma and platelet factor-4 (PF-4) during the headache that coincided with increased plasma serotonin levels. High serum serotonin levels which is due to a temporary disturbance (transient) of the turnover or the uptake of serotonin. Jensen and Hindberg in 1994 said that the increase in serotonin levels during tension-type headache attacks show a secondary response because of the pain. The serotonin receptors are distributed throughout the central nervous system. Increased serum levels of serotonin also stimulates afferent activity of muscles and explain why pericranial tenderness found on tension-type headache. Changes in serotonin concentrations associated with the emergence of tenderness perikranial and impaired regulation of central pain in tension-type headache.[20]

Bendsten (2000) said that there is some mechanism for the occurrence of tension-type headache : sensitization of nociceptors miofascial, sensitization of neurons order both at the level of the dorsal horn of the spinal cord or the nucleus trigeminalis, sensitization of neurons supraspinal, and decreased activity of anti-nociceptive of structure supraspinal. Cathcart et al in 2010 said that the pathophysiology of tension-type headache include both peripheral and central sensitization, disorders of the inhibitory mechanisms of pain and / or improvement of the process of psychological pain in patients with tension-type headache. In frequent episodic tension-type headache expected to occur both peripheral and central sensitization but their decreased activity or anti-nociceptive pain disorders inhibition mechanism may still not occur in frequent episodic tension-type headache and occurs more often in chronic tension-type headache.[12,22]

The sensation of pain is not only modulated through the ascending transmission from the periphery to the cerebral cortex, but also a segmental modulation and descending control of the higher center. This inhibitory control starts from the cortex, thalamus, and brainstem (periaquductal gray (PAG), the raphe nuclei, locus ceroleus. The main neurotransmitters that play a role in central pain inhibition is serotonin, noradrenaline and endogenous opioids. From several studies it is known that there is a possibility of neurotransmitters other than serotonin plays a role in the inhibition of pain through spinal projection. Giving intrathecal noradrenalin causing analgesia in mice and the lesions that cause a decrease noradrenaline level may lead to hyperalgesia. In addition to noradrenaline, opioids also play a role in pain modulation components either ascending or descending component. In descending component, receptors that act is mu and kappa receptor. Mu receptors are found in the periaqueductal gray, dorsal root spinal nerve, and medial raphe nucleus with a high bulk density in the locus ceroleus. About 40% of the periaqueductal gray terminal is GABA-ergic. This is supported by the injection of $GABA_A$ receptor agonists on the periaqueductal gray and dorsal spinal nerve root may lead to hyperalgesia and block the action of antinociception. Administration $GABA_A$ receptor antagonist would cause hipoalgesia. Acetylcholine is expected to also play a role, but the role of acetylcholine in the inhibition of pain is still not widely known role.[23]

Study conducted by Bendsten in 2000 on the effect of amitriptyline and citalopram (a selective serotonin reuptake inhibitor) in patients with chronic tension-type headache not only strengthen that serotonin that contribute to pain but also other neurotransmitters. Amitriptyline lowering headache for 30% compared with placebo while citalopram only about 12%. Amitriptyline was also significantly decreased the duration of headache, headache frequency, and the need for analgetics. Amitriptyline not only have effect on the reuptake of noradrenaline but also to the serotoninergic receptors, adrenergic, cholinergic, and histaminergik while Citalopram is only a selective serotonin reuptake inhibitor.[12]

We found 14 subjects (45.2%) with pericranial tenderness in cases groups and 5 subjects (16.1%) in the control groups. From the bivariate analysis, there is a significant association between tenderness perikranial and frequent episodic tension-type headache($p = 0.013$). This is consistent with Fernandez-de-las-Penas et al study at 2006. They found pericranial tenderness either in cases groups (subjectss with frequent episodic tension-type headache) or in control groups. Pericranial tenderness not only found in cases groups but also in control groups.[24]

Pericranial tenderness is a nociceptive stimuli that act to cause and spread the pain. Pericranial tenderness is associated with activation of nociceptors in the muscle by releasing some endogenous substances, including neuropeptides and inflammatory mediators. Some studies suggest that the concentration of bradykinin, CGRP, substance P, TNF-α, interleukin (IL) 1β, IL-6, IL-8, serotonin, and norepinephrine is found elevated in pericranial tenderness. Pericranial tenderness will cause peripheral sensitization. Beside that Pericranial tendernsess

may also lead to central sensitization. Several studies said that pericranial tenderness will lead to increased activity in the brain (primary and secondary somatosensory cortex, the inferior parietal cortex, and anterior and medial insula). The existence of both peripheral and central sensitization can contribute to the occurrence of this pericranial tenderness. This can explain why the pericranial tenderness correlated with frequent episodic tension-type headache.[25]

The strength of this study are not many researchers who studied the relationship of sleep quality with frequent episodic tension-type headache especially in Indonesia. The weakness of this study is undetermined factors that cause poor sleep quality in medical students.

5. Conclusion

Poor sleep quality statistically significant to increase the risk of frequent episodic tension-type headaches on medical students in Udayana university of Bali.

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