Original Article

Does Sleep Quality Affects the Immediate Clinical Outcome in Patients Undergoing Coronary Artery Bypass Grafting: A Clinico-biochemical Correlation

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Abstract

Objective: Poor sleep quality is emerging as high prevalence among the patients suffering from cardiometabolic disturbances. The vascular polypeptide endothelin 1 (ET-1) is involved in many of the health disorders. However, its potential involvement in patients having poor sleep quality along with cardiovascular problem is limited. The present study was formulated to conduct a prospective analysis of the relationship between ET-1 and in hospital outcome in sleep disorder patients undergoing routine coronary artery bypass grafting (CABG). **Methods:** A total of 156 patients were enrolled and divided into two groups based on the Pittsburg Sleep Quality Index (PSQI) of ≤5 (Group I, n = 101) or >5 (Group II, n = 55). Blood sample was collected before anesthesia induction (ET-1a) and at 48 h (ET-1b) to analyze the plasma ET-1 and blood sugar level. The patients were monitored for any intraoperative adverse events and postoperative complications during their hospital stay. **Results:** Both groups were comparable in relation to age, sex, incidence of smoking and alcohol consumption. The distribution of comorbid conditions was also similar in both groups. The ET-1 level was higher in Group II than Group I before anesthesia induction as well as 48 h postoperatively (4.5 ± 1.75 vs. 10.61 ± 9.3, P = 0.001; 2.08 ± 1.3 vs. 8.3 ± 9.86, P = 0.0001, respectively). The Group II patients had a longer duration of mechanical ventilation (14.6 ± 12.05 vs. 10.1 ± 8.19, P = 0.001), Intensive Care Unit stay (2.08 ± 0.95 vs. 2.7 ± 1.45, P = 0016) and hospital stay (5.98 ± 1.73 vs. 7.8 ± 3.66, P = 0.0001, respectively). The high number of patients from Group II required inotrope and intra-aortic balloon pump support while compared with Group I ($P \leq 0.05$ in each). The overall postoperative complication rate was significantly higher among patients with PSQI of >5 (Group II) except the rate of infection and neurological complications which was similar among both group of patients. The postoperative in hospital mortality was nil in Group I and 3.6% in Group II (P = 0.05). There was a strong relationship between PSQI and ET-1 at both the time points. **Conclusion:** Poor sleep quality associated with a higher incidence of adverse perioperative events in patients undergoing elective CABG. There exists a potential link between poor sleep quality and ET-1 in these groups of patients.

Keywords: *Coronary artery disease, endothelin-1, sleep quality*

Introduction

Good sleep is an important aspect of health. Poor sleep (difficulty in maintaining sleep, having an intermittent awakening, and early awakening) are increasingly common in recent days with a high prevalence in patients suffering from coronary artery disease, hypertension, and metabolic disorders.[1,2] Various mechanisms have been explored and suggested as a potential link between poor sleep pattern and negative health outcomes.[3] Nevertheless, the existing information is limited, and the pathophysiological pathway between poor sleep patterns and outcomes from cardiometabolic diseases remain unclear. Endothelin-1 (ET-1), a potent vasoconstrictor, is released mainly by vascular endothelial cells under the influence of hypoxia and other stimuli. ET-1 is related to endothelial dysfunction, as well as arterial and pulmonary hypertension. There is limited information on the level of poor sleep quality and this vascular peptide. Moreover, no information exists studying the relationship of this biomarker in patients with poor sleep quality who are suffering from ischemic heart disease. The aim of the present study was prospectively to study if there exists a relationship

How to cite this article: Choudhury M, Gupta A, Hote MP, Kapoor PM, Khanna S, Kalaivani MV, *et al.* Does sleep quality affects the immediate clinical outcome in patients undergoing coronary artery bypass grafting: A clinico-biochemical correlation. Ann Card Anaesth 2017;20:193-9.

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Access this article online

Website: www.annals.in

DOI: 10.4103/aca.ACA_30_17

Quick Response Code:

between sleep quality, plasma levels of ET-1, and clinical outcome in patients undergoing coronary artery bypass grafting (CABG).

Primary outcome measures

The relationship between ET-1 and poor sleep quality.

Secondary outcome measures

The duration of mechanical ventilation, Intensive Care Unit (ICU) stay, hospital stay, and postoperative outcome parameters including complications among the patients with good or poor sleep quality.

Methods

Study design

This is prospective clinical study.

Study population

The study was started only after approval from hospital ethical committee and written informed consent from the participants. Within a period of past 4 years, a total of one hundred and fifty-six patients aged more than 40 years suffering from coronary artery disease undergoing elective CABG were enrolled in the present study. The exclusion criteria's were: patients on mechanical ventilation, ventricular ejection fraction <55%, uncontrolled endocrinological disorder, and any other organ dysfunction or taking medication which can affect plasma ET-1 level. Detailed information about medical history was collected. Routine laboratory profile, pulmonary function test, echocardiography, and coronary angiography were obtained from each patient.

Assessment of sleep and related factors

Subjective measurement of sleep was done using the tool Pittsburg Sleep Quality Index (PSQI) questionnaire during their 2nd visit (2–3 days before admission).[4] In this, the sleep quality was assessed by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction over the last 1 month.[5] Each component is scaled from 0 to 3, with 0 representing a normal and 1–3 an abnormal condition. The sum of scores for these seven components yields a total score which ranges between 0 and 21. A total score >5 signifies disordered sleep. This questionnaire has a sensitivity of 89.6% and a specificity of 86.5% in distinguishing good and poor sleepers. Smoking habit was defined as never, previous, or current.

(Current smokers were defined as those persons who smoked daily at the time of the study but 1 week before. Ex-smokers were persons who had smoked daily and had given it up. Nonsmokers were persons who had never smoked). Height, weight, body mass index, and vital parameters were measured before administration of anesthesia.

Blood sample collection

Ten ml of blood was collected before anesthesia induction and 48 h after surgery using ethylenediaminetetraacetic acid as an anticoagulant. It was centrifuged to isolate plasma fraction. Plasma was immediately frozen at −70° for assay at a later date. Commercially available enzyme-linked immune sorbent assay kits were used to determine plasma ET-1 level (Assay Designs, Inc., 5777, Hines drive, Ann Arbor, Michigan 48108 USA). Blood sugar estimation was done at the same time.

Anesthesia management

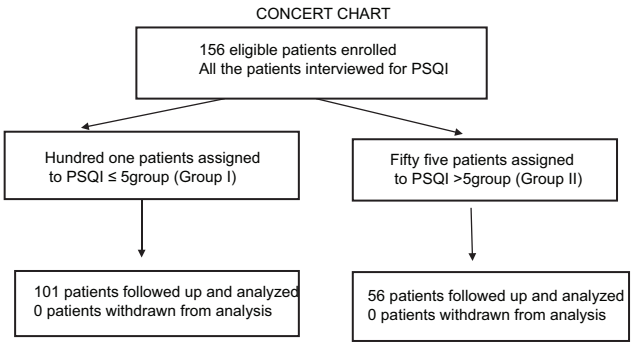
All preoperative cardiac medications were continued till the morning of surgery except angiotensin-converting enzyme inhibitors. All the patients received oral diazepam 10 mg in the night before surgery. Intramuscular morphine 0.2 mg/kg and promethazine 25 mg were given as premedication 1 h before anesthesia induction. Routine monitoring as per any other cardiac surgical patients was done. All the patients were induced with intravenous fentanyl 4 μ/kg and thiopentone sodium 3–5 mg/kg. Rocuronium bromide 0.6 mg/kg was administered intravenously to facilitate tracheal intubation. All of them were mechanically ventilated with 50% air-oxygen mixture to maintain an end-tidal carbon dioxide between 35 and 40 mmHg. CABG was done under routine cardiopulmonary bypass (CPB), moderate hypothermia and moderate cold blood cardioplegia.

Statistical analysis

Before starting the analysis, the patients were divided into two groups depending on the PSQI score of ≤5 (Group 1, n = 101) or >5 (Group II, n = 55). Data were presented as mean ± standard deviation (SD)/median (range) or number %. The difference in means/medians of continuous variables between Group I and Group II was estimated using Student's t-test for independent samples/Wilcoxon rank-sum test since the data were not normally distributed. Categorical variables between the groups were compared using Chi-square test. The association between ET-1 level and smoking was analyzed using Krusal–Wallis test. The correlation between ET-1 and PSQI score was tested using Spearman–rank correlation. In all case, the $P < 0.05$ was considered as statistically significant. For analyses of continuous data, to detect differences between the groups Wilcoxon rank-sum test was used. All analyses were performed using STATA 9.0 (Stata Corp LP; College Station, TX, USA).

Results

The following concert chart shows the detailing of the patient allocation and analysis.



The demographics and clinical data of all patients are summarized in Table 1. Both groups were comparable in relation to age, sex, incidence of comorbid conditions, duration of surgery, CPB time, and aortic cross-clamp time (AOxCl) [Table 2]. The incidence of smoking and alcohol consumption was also similar in between the groups [Table 2].

The duration of mechanical ventilation, ICU stay and hospital stay was significantly shorter in Group I compared to Group II with a mean ± SD of 10.10 ± 8.19 versus 14.76 ± 12.05 h, 2.08 ± 0.95 versus 2.70 ± 1.45 days and 5.98 ± 1.73 versus 7.83 ± 3.66 days; and $P = 0.001$, 0.0016, and 0.0001, respectively [Table 2]. The relationship between Pittsburg sleep quality index, postoperative complication and ET-1 level at two different points is described in Table 1. The Group II patients experienced a higher overall complication rate compared to Group I (24 [43.43%] vs. 3 [2.9%], $P = 0.0001$) [Table 3]. High number of patients from Group II required dopamine, adrenaline and more than two inotropes compared to Group I [Table 3], ($P = 0.0001$, 0.0001, and 0.017, respectively). However, the groups did not differ in the context of neurological complication and rate of infection (0 vs. 4, $P = 0.01$ and 3 [42.86%] vs. 4 [54.15%], $P = 0.22$), [Table 3], respectively. The incidence of perioperative arrhythmia was significantly higher in Group II patients (16 [20.64%] vs. 7 [6.93%], $P = 0.0001$), [Table 3]. Seven patients (12.72%) from Group II needed intra-aortic balloon pump support while none from Group I required the same [$P = 0.0001$, Table 3]. A total of six patients from Group II suffered from myocardial dysfunction and low cardiac output syndrome (2 cases, 3.63%) leading to prolong ICU stay. Renal dysfunction occurred in 4 cases, (7.27%) in these patients. Whereas, none of the patients from Group I had any of such problems. These figures though statistically significant ($P = 0.056$ and 0.006, respectively) clinically not relevant. No mortality was observed in Group I while two patients (3.63%) from Group II died due to myocardial failure [$P = 0.05$, Table 3]. The preoperative ET-1 levels though clinically high in previous smokers (8.82 ± 7.81 pg/mL, 5.8 ± 4.88 pg/mL, and 6.51 ± 4.30 pg/mL, respectively) when compared to nonsmokers and who smoked during recent past were not statistically significant ($P = 0.64$). A similar finding was elicited for the postoperative values. No significant difference was noted in the ET-1 level among the nonalcoholic and alcoholics at both time points (6.18 ± 5.16 pg/mL vs. 7.24 ± 6.53 pg/mL, $P = 0.64$ and 4.04 ± 6.29 pg/mL vs. 5.05 ± 7.67 pg/mL, $P = 0.6$, respectively). We found a strong relationship between PSQI and ET-1 level at both time points ($r = 0.6265$, $P = 0.0001$ and $r = 0.4116$, $P = 0.0001$, respectively); [Figures 1 and 2]. Spearman correlation test revealed no relationship between hematocrit ($r = -0.002$, $P = 0.97$) and blood sugar value ($r = 0.05$, $P = 0.49$) to that ET-1 level in both group of patients. Relationship between Pittsburg Sleep Quality Index, postoperative complications and Endothelin 1 level at two different time points is shown in Table 4.

Table 1: Summarized statistical data showing distribution of demographics and clinical characteristics of the patients (n=156)

Parameter	Mean±SD/*n* (%)‡
Age (year)	58.9±9.3
Sex (male:female)‡	142:14
Height (cm)	170.7±7.3
Weight (kg)	69.7±12.3
BMI (m^2)	23±5.7
BSA	1.8±0.14
Smoking‡	
Never	33 (21.15)
Previous	27 (17.30)
Current	23 (14.74)
Alcohol‡	
Yes	120 (79.92)
No	36 (23.07)
MI (yes:no)‡	27 (17.31):129 (82.69)
Hypertension (yes:no)‡	49 (31.4):107 (68.5)
DM (yes:no)‡	27 (17.31):129 (82.69)
Number of coronary vessel involved‡	
Single	0
Double	0
Triple	156 (100)
PSQI (≤5:>5)‡	27 (17.31):129 (82.69)
ET-1a (pg/mL)	6.43±5.5
ET-1b (pg/mL)	4.2±6.6
Duration of surgery (min)	313.9±53.2
CPB duration (min)	81.9±51.5
Aortic cross clamp time (min)	50.8±15
Duration of mechanical ventilation (h)	11.8±9.9
Duration of ICU stay (days)	2.30±1.19
Duration of hospital stay (days)	6.6±2.7

All data are presented as mean±SD unless otherwise stated. ‡Data expressed in *n* (%). BMI: Body mass index, BSA: Body surface area, MI: Myocardial infarction, DM: Diabetes mellitus, PSQI: Pittsburg Sleep Quality Index, CPB: Cardiopulmonary bypass, ICU: Intensive Care Unit, SD: Standard deviation, ET-1a: Before anesthesia induction, ET-1b: 48 h postoperatively, ET-1: Endothelin 1

Table 2: Comparison of demographics and clinical profile of patients in both the groups by Chi-squire test

Parameters	Group I, PSQI ≤5 (*n*=101)	Group II, PSQI >5 (*n*=55)	*P*
Age (year)	59.1±9.3	58.4±9.3	0.66
Sex (male:female)	92:9	50:5	
Height (cm)	171.6±7.08	169.05±7.62	0.03
Weight (kg)	69.77±11.09	69.97±12.09	0.23
BMI (kg/m^2)	23.78±4.17	23.84±4.51	0.45
BSA (m^2)	1.81±0.18	1.81±1.15	0.34
Smoking‡			
Never	73 (72.28)	33 (60)	0.25
Previous	16 (15.84)	11 (20)	
Current	12 (11.88)	11 (20)	
Alcohol‡			
No	79 (78.22)	41 (74.55)	0.60
Yes	22 (21.78)	4 (25.45)	
MI (yes)‡	5 (4.95)	12 (21.81)	0.272
DM (yes)‡	29 (28.71)	10 (18.18)	0.14
Hypertension (yes)	34 (32.67)	15 (27.27)	0.41
Ejection fraction	57±11.5	56±12.3	0.61
FEV_1	69.34±12.45	69.45±11.1	0.95
ET-1 (pg/mL)	4.15±1.75	10.61±97.3s	0.0001
ET-1b (pg/mL)	2.08±1.30	8.30±9.86	0.0001
Duration of surgery (min)	314±53	313.72±53.26	0.97
CPB duration (min)	85.7±0.7	86.3±0.3	0.81
Aortic cross clamp time (min)	50.48±15	51.54±15.25	0.67
Duration of mechanical ventilation (h)	10.10±8.19	14.76±12.05	0.001
Duration of ICU stay (days)	2.08±0.95	2.70±1.45	0.0016
Postoperative complication (yes)‡	3 (2.9)	24 (43.43)	0.0001

P<0.05 implies significant difference compared to normal range, *P*<0.001implies highly significant difference compared to normal range. All data are presented as mean±SD unless otherwise stated. ‡Data expressed in *n* (%). BMI: Body mass index, BSA: Body surface area, MI: Myocardial infarction, DM: Diabetes mellitus, PSQI: Pittsburg Sleep Quality Index, CPB: Cardiopulmonary bypass, ICU: Intensive Care Unit, ET-1a: Before anesthesia induction, ET-1b: 48 h postoperatively, FEV_1: Forced expiratory volume 1 s, SD: Standard deviation, ET-1: Endothelin 1

Table 3: Relationship between Pittsburg Sleep Quality Index with co morbid condition, inotrope requirement, intra-aortic balloon pump use and outcome parameters

Parameters	PSQI ≤5 (*n*=101)	PSQI >5 (*n*=55)	*P*
Female sex	6 (5.94)	8 (14.55)	0.072
MI	15 (14.85)	12 (21.82)	0.27
Hypertension	34 (33.66)	15 (27.27)	0.41
DM	29 (28.71)	10 (18.18)	0.14
Postoperative complication	5 (4.95)	22 (40)	0.001
Dopamine	4 (3.9)	9 (16.36)	0.001
Adrenaline	0	9 (16.36)	0.001
>Two inotropes	0	3 (5.56)	0.017
IABP	0	7 (12.72)	0.001
Arrhythmia	7 (6.93)	16 (29.09)	0.001
Respiratory dysfunction	0	4 (7.2)	0.007
Infection	3 (2.9)	4 (7.2)	0.220
Myocardial dysfunction and low cardiac output syndrome	0	2 (3.63)	0.056
Neurological complication	0	1 (1.81)	0.17
Renal dysfunction	0	4 (7.2)	0.006
Death	0	2 (3.63)	0.05

P<0.05 implies significant difference compared to normal range, *P*<0.001implies highly significant difference compared to normal range. Data expressed in *n* (%). MI: Myocardial infarction, IABP: Intra-aortic balloon pump, PSQI: Pittsburg Sleep Quality Index, DM: Diabetes mellitus

Table 4: Relationship between Pittsburg Sleep Quality Index, postoperative complications and Endothelin 1 level at two different time points

Parameters	ET-1a	Median (range)	*P*	ET-1b	Median (range)	*P*
PSQI	≤5	4.22 (0-11)	0.0001	≤5	2.1 (0.39-8.44)	0.0001
	>5			>5		
IABP	Yes	16.33 (9.11-30.33)	0.0001	Yes	20.22 (2.72-35.25)	0.002
	No	4.5 (0-36.54)		No	2.2 (0.39-45.23)	
Arrhythmia	Yes	11 (3.01-36.54)	0.0001	Yes	5.65 (0.5-45.23)	0.0001
	No	4.32 (0-21.33)		No	2.2 (0.39-26.35)	
Infection	Yes	11.83 (3.42-30.33)	0.008	Yes	2.72 (0.56-35.25)	0.37
	No	4.45 (0-36.54)		No	2.3 (0.39-45.23)	
Respiratory problem	Yes	21.26 (15.1-30.33)	0.001	Yes	11.3 (0.45-11.2)	0.002
	No			No		
Cardiac problem	Yes	18.78 (14.45-23.11)	0.026	Yes	20.85 (18.58-23.12)	0.02
	No	4.69 (0-36.54)		No	2.3 (0.39-45.23)	
Neurological complications	Yes	9.11 (0-9.11)	0.29	Yes	8.22 (8-8.22)	0.7
	No	4.56 (0-36.54)		No	2.3 (0.39-45.23)	
Renal complications	Yes	21.26 (17.77-30.33)	0.001	Yes	21.67 (12.63-35.25)	0.001
	No	4.45 (0-36.54)		No	2.25 (0.39-45.23)	
Death	Yes	11.47 (8.5-14.45)	0.07	Yes	14.72 (6.32-23.12)	0.64
	No	4.5 (0-36.54)		No	2.3 (0.39-45.23)	

Data are presented as median range (IQR). $P<0.05$ implies significant difference compared to normal range, $P<0.001$implies highly significant difference compared to normal range, PSQI: Pittsburg Sleep Quality Index, IABP: Intra aortic balloon pump, IQR: Interquartile range, ET-1: Endothelin 1, ET-1a: Before anesthesia induction, ET-1b: 48 h postoperatively

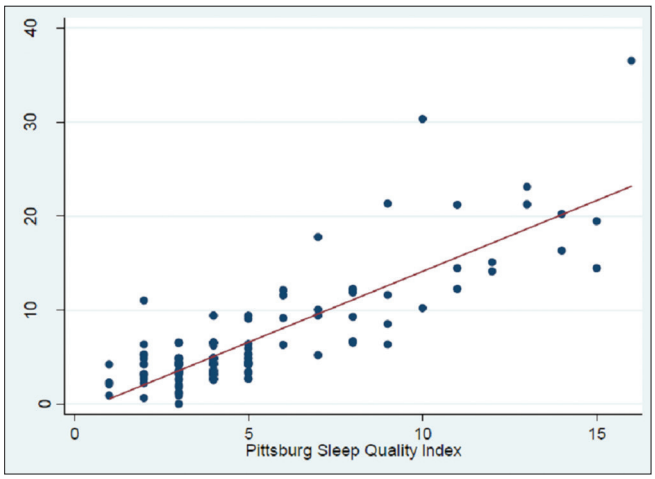


Figure 1: The relationship between Pittsburg Sleep Quality Index and Endothelin 1 level before surgery. *r* = 0.6265, *P* = 0.0001

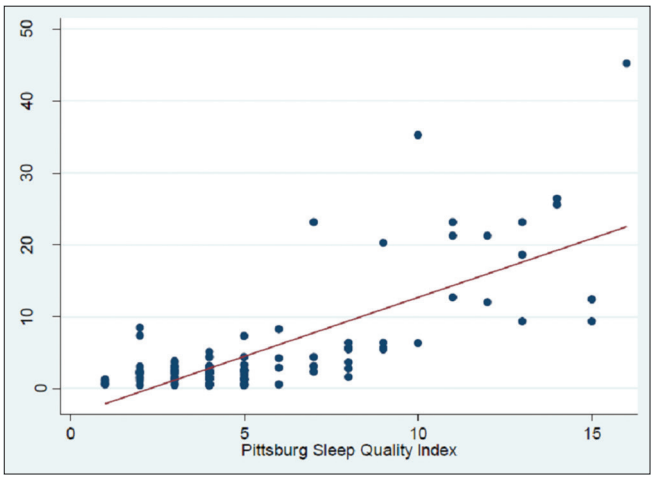


Figure 2: The relationship between Pittsburg Sleep Quality Index and Endothelin 1 level 48 h after surgery. *r* = 0.116, *P* = 0.0001

Discussion

Recent evidence is that disturbances in sleep play a role in morbidity in chronic conditions. However, the relationship between sleep process and disease progression is often unclear. Hence, it is important that the outcome of such disease states should be studied to determine whether sleep affects merely the disease outcome or it is someway casually related. Sleep is a complex pnenotype and as such it is possible that there are numerous biochemical factors or genes which may have a number of effects on individual sleep pattern.

In this study, a strong relationship between poor sleep quality and ET-1 level was associated with adverse postoperative events in patients undergoing CABG.

Poor sleep is frequently associated with repeated arousals, daytime sleepiness, or history of intake of sleeping pills.[6] There is an emerging recognition of the association of this disorder with metabolic problems, coronary artery disease, hypertension, and congestive cardiac failure.[7,8] However, no information exists on the determinants of poor sleep quality and in hospital outcome among the patients undergoing elective CABG.

The endothelium is the common target of most of the organ dysfunction. It can produce a large variety of different molecules which act as agonist and antagonist, therefore balancing their effect on opposite direction. ET-1 is a peptide hormone which is secreted predominantly by endothelial cells under the influence of stimuli such as hypoxia and ischemia.[9,10] Eitel *et al*. and Belaidi *et al*. described the possible association between ET-1 in the prognosis of acute myocardial infarction.[11,12] However, Palacín *et al*. demonstrated a lack of association between ET-1 gene variant and myocardial infarction.[13] High ET-1 level in both the patients who had or not an episode of myocardial infarction in our patients suggests that some other endothelium modulating factor is contributing to this fact. A similar finding was also observed among the patients who were either suffering or not from hypertension. Palmer and associates found a strong negative association between smoking, alcohol intake, and sleep duration in men. However, they could not elicit an equivalent association between drinking and smoking and reported sleep quality.[14] Lexcen and Hicks in a questionnaire study demonstrated that cigarette smoking has been associated with delayed sleep onset and diminished sleep duration.[15] However, their data were difficult to interpret because smokers also used the significantly greater amount of alcohol and caffeine. Phillips and Danner in a random sample of 1000 mail survey found that cigarette smokers were significantly more likely than nonsmokers to report problems in going to sleep, staying asleep, daytime sleepiness, minor accidents, depression, and high daily caffeine intake.[16] We could not found any association between poor sleep quality and smoking in our population group. Small sample size can be a contributing factor to such a result. An elevated level of ET-1 was found 30 min after smoking in a group of volunteers as noted by Haak *et al*.[17] Alcohol affects endothelial function and increased the level of ET-1 in a study by Soardo *et al*.[18] The elevated levels of ET-1 in both the patient groups who have or have not the habit indicates that factors other than these are also responsible for endothelial dysfunction. Okun *et al*. found a link between disturbed sleep and inflammatory markers in pregnant patients and association between inflammation and increased morbidity in this group of population.[19] Rikimaru *et al*. demonstrated that ET-1 is strongly expressed in inflamed periodontal tissue and is involved in the expression on interleukin-1 beta, an important cytokine during the inflammatory process.[20] From these studies, it cannot be ruled out that poor sleep quality alters endothelial function.

Conclusion

The prevalence of hypertension was 87.1% in "poor sleepers" subjects versus 35.1% in "good sleepers" as noted by Fiorentini *et al*.[21] However, this fact was not true for our patients. Suzuki *et al*., in a population-based study observed that although no clear association was found between sleep quality and mortality, long sleep duration was associated with higher risk of cardiovascular disease-related mortality among those with poor sleep quality.[22] The authors evaluated the overall sleep quality rather than long sleep duration in their study and found the former as an associate to mortality.

Acknowledgments

We would like to thank Dr. Sunil Nanda and Staff nurse Lovely and Elliyama for the collection of PSQI questionnaire data from the patients. None of them are responsible for analysis or interpretations put forth in this article.

Financial support and sponsorship

This study was supported by Institute research grant.

Conflicts of interest

There are no conflicts of interest.

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