

Assessment of sleep pattern and quality before and after liver transplantation using different methods

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ABSTRACT

Background/Aims: Sleep disorders (SDs) are frequently seen in patients with liver cirrhosis. Polysomnography (PSG), actigraphy, and electroencephalogram (EEG) are the common objective methods to diagnose SDs. The most commonly used subjective methods are the Pittsburgh sleep quality index (PSQI) and Epworth sleepiness scale (ESS). We aimed to evaluate the effect of liver transplantation (LTx) on SDs using a combination of objective (PSG and EEG) and subjective (PSQI and ESS) methods.

Materials and Methods: A total of 18 patients with cirrhosis on an LTx waiting list were included in this study. Patient clinical status and biochemical parameters were evaluated. All patients completed the validated Turkish forms of the PSQI and ESS before and 9 months after LTx. All patients underwent EEG and PSG before and 9 months after LTx.

Results: In total, 18 patients with liver cirrhosis (men: 12; 66.7%, mean age: 53.22±10.43 years) were included in this study. Pretransplant mean PSQI and ESS scores were 8.4±3.11 and 7.28±3.89, respectively; 9-month posttransplant mean PSQI and ESS scores were 4.5±2.8 and 4.72±2.91 ($p<0.01$), respectively. Before transplantation, metabolic encephalopathy was detected in 6 patients by EEG, whereas metabolic encephalopathy was detected in only 1 patient posttransplant. Posttransplantation PSG sleep duration (all stages) increased relative to pretransplant PSG values. Sleep latency and rapid eye movement latency were found to be reduced compared to the pretransplant values.

Conclusion: This pilot study compared SDs in patients with pre- and post-LTx by combining the subjective and objective methods. Significant SD improvements were found at the 9th month.

Keywords: Sleep disorders, liver cirrhosis, EEG, polysomnography, PSQI, ESS

INTRODUCTION

Sleep disorders (SDs) are more common in patients with cirrhosis than healthy adults. SDs adversely affect the daily lives and quality of life (QOL) of patients with cirrhosis. Disease-related disorders, pain, poor sleep hygiene, sleep-warding drug treatments, pruritus, and fatigue are generally the most frequent factors causing sleepiness in patients with cirrhosis. These factors may be pathophysiologically related to the existing chronic liver disease or impaired liver function. In some studies, however, SDs have been detected in compensated patients with cirrhosis without tense ascites and diuretic therapy. Major complaints in patients with cirrhosis with SD are prolonged time to fall asleep (short sleep latency [SL]), shortened sleep duration, excessive daytime sleepiness

(EDS), poor sleep quality, and frequent nocturnal awakening. Insomnia in patients with cirrhosis is reported to be 26%–42% in various studies. The most frequent finding by polysomnography (PSG) studies is decreased rapid eye movement (REM) duration (1–7).

It is thought that SD is the first clinical manifestation of hepatic encephalopathy (HE). HE is classified as overt and covert. Covert HE corresponds to grade I according to the West Haven Criteria. Covert HE affects 80% of the compensated and decompensated patients with cirrhosis. On average, 30%–45% of the patients on the liver transplant list undergo overt HE at least once while waiting for liver transplantation (LTx). Cognitive deficits caused by HE before LTx are often cured after LTx. SD is common in HE

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population before and after LTx. Recent studies indicate that posttransplant patients have improved general QOL. Neurological complications are more common in liver transplant than in other solid-organ transplants. Neurological complications are fewer after living donor LTx than cadaveric LTx. The most important factors affecting the cognitive deficits after LTx are pretransplantation HE status, advanced anoxic/ischemic brain injury during surgery, osmotic myelinolysis, immunosuppressive toxicity, and comorbid diseases. These are prevalent in this patient group before and after transplantation. However, studies investigating SD in liver transplant recipients are limited (8-14).

In this prospective study, we aimed to compare pre and posttransplant sleep quality and SDs in patients with liver transplant using a combination of objective and subjective methods, such as the Pittsburgh sleep quality index (PSQI), PSG, and electroencephalogram (EEG).

MATERIALS AND METHODS

Patient population

A total of 18 patients with liver cirrhosis aged 18–70 years who underwent LTx between January 2017 and June 2017 were included in this prospective study. Patients with severe renal insufficiency, taking antidepressant/antipsychotic medications as well as with alcohol-induced liver cirrhosis who had consumed alcohol within the prior 6 months, cerebrovascular disease, severe chronic obstructive pulmonary disease and severe congestive heart disease, severe diabetes mellitus, neurological deficits other than HE (such as Parkinson's disease and dementia), and patients lacking the physical and mental capacity to answer the questionnaires were excluded. Before LTx, all the patients completed PSQI and ESS forms and underwent EEG and PSG. PSQI and ESS forms were completed, and EEG and PSG were performed on each patient during the 9th month after LTx. Pre- and post-LTx results were compared.

MAIN POINTS

- We aimed to evaluate the effect of liver transplantation (LTx) on SDs using a combination of objective (PSG and EEG) and subjective (PSQI and ESS) methods in this prospective study.
- This is the first study which compared SDs by subjective and objective methods in pre and posttransplant patients.
- Posttransplant results revealed significant improvements in SDs. Future studies with larger populations are needed to enlighten this era.

Pittsburgh sleep quality index questionnaire

This questionnaire is useful for evaluating sleep quality and sleep disturbances over the preceding month and to detect "good" and "poor" Sleepers. PSQI contains 19 items, which cover 7 components, including subjective sleep quality, SL, sleep duration, sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. Each question is scored from 0 to 3, where a score of 3 represents the negative extreme. These component scores are then summarized to provide the total PSQI score (range: 0-21); scores of >5 identify "poor sleepers." Completing the questionnaire takes approximately 10 min, and scoring takes 5 min. We used a validated Turkish version of the PSQI in this study (15, 16).

The PSQI questionnaire was completed by patients in the presence of a doctor. All patients filled these forms pretransplant and posttransplant in the 9th month.

Epworth's sleepiness scale

ESS was used to detect the subjective levels of EDS. ESS asks the patients to rank their likelihood of dozing in 8 different situations, with "0" indicating "would never doze" and "3" indicating "high chance of dozing." Higher scores (0-24) indicate increasing levels of EDS, and a score of >10 resembles clinically significant EDS. We used a validated Turkish version of the ESS in this study (17, 18).

The ESS questionnaire was completed by the patients in the presence of a doctor. All the patients filled these forms pretransplant and posttransplant in the 9th month.

Electroencephalography

For each patient, a spontaneous eye-closed waking EEG was recorded with digital EEG equipment (Nihon Kohden Corporation, Nishiochiai, Shinjuku-ku, Tokyo, Japan); 21 compatible silver/silver chloride electrodes were affixed to the scalp according to the International 10-20 system. All the electrodes were grounded and referenced at the frontopolar and ear points, respectively. The recording was done for 20-30 min, and the raw data were filtered between a low frequency, 0.5 Hz, and a high frequency, 70 Hz. Impedance was lower than 5 kΩ. Each patient underwent EEG before and 9 months after LTx. Each imaging was done under the control of 2 electroneurophysiology specialists who were blindfolded to the clinical findings and to each other. The results of the EEGs were reported by the same 2 specialists, and the readings were also assessed according to the Parsons-Smith classification (19).

Polysomnography

PSG was performed using the Alice 5 Polysomnography System (Respironics Inc., Murrysville, PA, USA) before and 9 months after LTx. PSG including 6-channel EEG (C3-A, C4-2, O1-A2, O2-A2, F3M3, and F4M1), 2 channel EOG (E1M2 and E2M1), submental electromyography (EMG), tibialis anterior EMG, nasal airflow, thoracic and abdominal respiratory movement monitoring, electrocardiography, oxygen saturation monitoring, and nightly polygraphic sleep monitoring with synchronous video recording was performed on all the patients. Hypopnea assessment was performed according to the American academy of sleep medicine (AASM) task force scoring guidelines (20). The taskforce reached consensus on a definition of hypopnea in adults using a 30% drop in the nasal pressure expulsion for 10 s or greater associated with ≥3% desaturation.

According to the AASM criteria, <5 Apnea-hypopnea index (AHI) events/hour is normal; for 5–15 AHI events/hour, the sleep respiratory disorder is classified as mild; 16-30 AHI events/hour is moderate; and >30 AHI events/hour is severe (20).

All the patients were informed about the experiment protocol, and verbal and written approvals were obtained. The study protocol was approved by our ethics committee. The study was conducted in accordance with the Helsinki Declaration and the European guidelines for good clinical practice.

RESULTS

Demographic characteristics of the 18 patients with liver cirrhosis (men: 12, 66.7%; age: 53.22±10.43 years) are presented in Table 1 and Figure 1.

According to the Child-Pugh classification, 6 (33.3%) of the 18 patients were classified as group A, 10 (55.6%) were classified as B, and 2 (11.1%) as C.

PSQI versus ESS

According to the pretransplant PSQI scores, 15 (83.4%) of the 18 patients showed a decrease in sleep quality, and 3 (16.6%) of the 18 patients had EDS according to the pretransplant ESS scores.

According to the posttransplant 9-month PSQI scores, 5 (17.8%) of the 18 patients showed a poor sleep quality, and 1 (5.4 %) of the 18 patients had EDS according to the posttransplant ESS scores.

Table 1. Demographics of the patients.

Parameters	Mean	SD
Age (year)	53.22	10.43
BMI	29.71	6.38
Child Score	7.89	1.88
MELD Score	14.61	5.36
AST (Iu/L)	65.28	38.74
ALT (Iu/L)	58.61	46.51
Albumin (gr/dL)	3.47	0.60
PT (second)	18.78	5.86
INR	1.56	0.43
Total Bilirubin (mg/dL)	2.90	2.59
Creatinine	0.78	0.27
Wbc (10 ³ /uL)	4.16	2.05
Hb (gr/dL)	11.01	2.52
Plt (10 ³ /uL)	104	630
Neu (%)	51.39	13.91

SD: Standard Deviation; BMI: Body mass index; MELD: Model For End-Stage Liver Disease; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; PT: Prothrombin Time; INR: International Normalized Ratio; Wbc: White Blood Cell; Hb: Hemoglobin; Plt: Platelets; Neu: Neutrophils

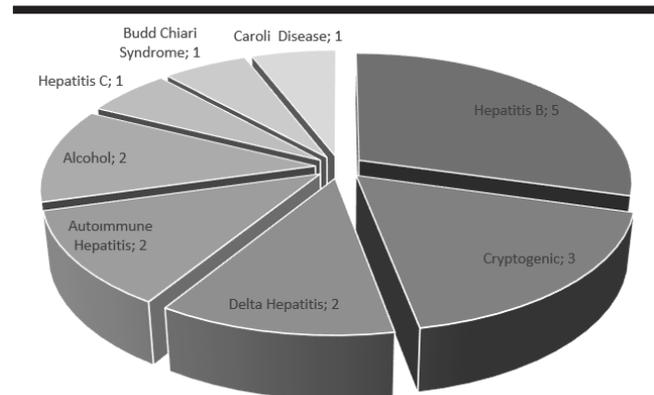


Figure 1. Etiology of cirrhosis

The pretransplant PSQI and ESS scores of the patients were 8.4±3.11 and 7.28±3.89, respectively. The post-transplant PSQI and ESS scores of the patients were 4.5±2.8 and 4.72±2.91, respectively. The differences between pre and posttransplant values were statistically significant (p<0.01) (Table 2).

Table 2. PSQI and ESS results.

	Pretransplantation n (%)	Posttransplantation n (%)	P
Poor Sleepers (PSQI>5)	15 (83.4%)	5 (17.8%)	p<0.05
Excessive Day- time Sleepiness (ESS>10)	3 (16.6%)	1 (5.4%)	p<0.05
PSQI Score (Mean)	8.4±3.11	4.5±2.8	p<0.05
ESS Score (Mean)	7.28±3.89	4.72±2.91	p<0.05

Electroencephalogram

In total, 10 of the 18 patients had a normal well-structured EEG with a symmetrical posterior basic rhythm >8 Hz and <13 Hz before and after LTx.

The EEG of 4 of the 18 patients had a predominant theta activity with random delta waves, roughly corresponding to Grade C of the Parsons–Smith classification, and after LTx, all the EEG tracings were normal.

Furthermore, 3 of the 18 patients had a low-frequency alfa rhythm (8 Hz) disturbed by random waves in the theta range over both hemispheres, corresponding to Grade B of the Parsons–Smith classification, and after LTx, 2 EEG readings were assessed as normal.

The EEG of 1 of the 18 patients had diffuse asynchronous theta and delta waves over both the hemispheres with triphasic waves, corresponding to Grade D–E of Parsons–Smith's classification, and after LTx, a low-frequency alpha rhythm with rare waves in the theta range over both the hemispheres was observed and assessed as Grade B of the Parsons–Smith classification.

Polysomnography

The duration of all the posttransplant PSG sleep stages increased relative to the pretransplant PSG values. SL and REM latency were reduced relative to the pretransplant values. The decrease in SL was statistically significant ($p<0.05$). The increase in N1 sleep duration was statistically significant ($p<0.05$). The comparison of patient PSG parameters between pretransplant and 9-month posttransplant is presented in Table 3.

DISCUSSION

SDs are common in patients with liver cirrhosis and may occur owing to a wide variety of factors, such as pain, rest-

lessness, fatigue, liver-disease-associated itching, poor sleep hygiene, medication use, and impaired liver function. Several mechanisms, such as hyperammonemia, HE, melatonin abnormalities, and circadian rhythm disorders, have been demonstrated in the pathophysiology of SDs in patients with cirrhosis. LTx is the most effective treatment for liver cirrhosis. SDs are expected to improve (as are other cirrhosis-related complications) after LTx. However, a small number of studies have found that SDs are still present in patients after LTx. Factors affecting posttransplantation SDs include pretransplantation HE type, advanced anoxic/ischemic brain injury during surgery, osmotic myelinolysis, immunosuppressive toxicity, comorbid diseases, and numerous posttransplant medications (1, 5, 7, 13, 14).

PSQI is the gold standard subjective method for sleep quality assessment. PSQI can easily distinguish poor sleepers from good sleepers. Samanta et al. detected 60 (60%) poor sleepers using PSQI in 100 patients with liver cirrhosis (21). Xiao et al. detected 214 (62.46%) poor sleepers using PSQI in 341 patients with liver cirrhosis (22). In our study, 15 (83.4%) of the 18 patients showed a poor sleep quality according to the pretransplant PSQI scores. The 9-month posttransplant PSQI scores identified 5 (17.8%) of the 18 patients with a decrease in sleep quality. Pretransplant and 9-month posttransplantation PSQI scores of the patients were 8.4 ± 3.11 and 4.5 ± 2.8 , respectively. The difference between pre and posttransplant values was statistically significant ($p<0.01$).

EDS is one of the most well-known parameters of sleep-wake abnormalities in patients with liver cirrhosis and is best evaluated by ESS. Samanta et al. investigated 100 patients with liver cirrhosis and detected EDS in 38 (38%) patients by using ESS (21). Montegnese et al. investigated 87 patients with liver cirrhosis and detected EDS in 21 (24.1%) patients (6). According to the pretransplant ESS scores in our study, 3 (16.6%) of the 18 patients had EDS. The 9-month posttransplantation ESS scores showed that 1 (5.4%) of the 18 patients had EDS. Pretransplant ESS and 9-month posttransplantation ESS scores of the patients were 7.28 ± 3.89 and 4.72 ± 2.91 , respectively. The difference between pre and posttransplantation values was statistically significant ($p<0.01$).

Subjective methods, such as PSQI and ESS, are very useful for screening, but they do not provide sufficient information about sleep structure and staging. The gold standard for SDs is PSG. Adults often need a total sleep time (TST) of about 7–9 hours. Sleep has 4 stages: NREM

Table 3. Evaluation of Polysomnography parameters before and after liver transplantation.

Parameters	Pre-Transplantation		Post- Transplantation		p
	Mean	SD	Mean	SD	
TRT (min)	362.78	37.80	374.50	21.57	0.142
TST (min)	242.40	53.08	273.33	52.12	0.133
Sleep Lat. (min)	40.56	29.77	22.14	24.06	0.049996
REM Lat.	145.08	89.30	113.53	66.75	0.184
SE	67.31	15.86	72.99	13.21	0.528
Arousals/h	27.84	22.47	16.23	16.12	0.170
Total Arousals	113.22	93.87	74.83	72.34	0.267
AHI	15.54	12.96	22.36	16.67	0.055
PLMI	20.87	40.20	22.47	44.09	0.774
Mean SpO2	96.06	2.92	96.11	1.49	0.811
Nadir SpO2	86.78	8.74	85.94	11.20	0.887
ODI	6.62	8.69	9.93	13.55	0.896
NREM (min)	207.94	44.58	236.94	47.85	0.058
REM (min)	28.81	17.03	36.56	22.75	0.513
REM (%)	11.40	5.57	13.31	7.66	0.528
N1 (min)	9.44	5.12	20.17	11.11	0.003
N1 (%)	4.29	2.94	8.14	6.00	0.028
N2 (min)	180.92	48.68	197.03	42.31	0.396
N2 (%)	74.48	10.45	72.19	8.64	0.557
N3 (min)	23.92	21.44	21.19	15.19	0.831
N3 (%)	10.18	9.24	7.28	4.40	0.349
Deep Sleep (min)	23.72	21.66	21.19	15.19	0.906

ST: Standard deviation; TRT: Total recording time; min: Minute; TST: Total sleep time; Sleep Lat: Latency to sleep onset; REM Lat: REM sleep latency; SE: Sleep efficiency; Arousals/h: Number of arousals per hour of sleep; AHI: Apnea-hypopnea index; REM: Rapid eye movement; NREM: Non-Rapid eye movement; PLMI: Periodic Limb movement index; Mean SpO2: Mean oxy-hemoglobin saturation; Nadir SpO2: Minimal oxy-hemoglobin saturation; ODI: Oxygen desaturation index N1:NREM Stage 1; N2: NREM Stage 2; N3:NREM Stages 3 and 4;

(nonrapid eye movement sleep; N1, N2, and N3) and REM sleep. A complete sleep cycle takes an average of 90–110 min. Usually there are 4 to 5 cycles per sleep time. A sleep cycle begins with NREM (N1, N2, N3) and continues with REM. TST is composed of 70%–80% NREM and 20%–25% REM sleep (20). Findings of recent sleep studies suggest that the informative value of sleep reference data in healthy individuals is limited because of the high interindividual and intraindividual variation in sleep

variables. Hertenstein et al. performed a PSG study with 206 healthy adults aged 19–73 years. According to this study, the reference levels of sleep stages were TST (min), 393.5±50.1 (women), 391.7±52.0 (men); N1 sleep (%), 8.9±4.6 (women), 9.2±4.9 (men); N2 sleep (%), 52.3±8 (women), 52.1±9.7 (men); REM sleep (%) 17.4±4.9 (women), 18.7±4.9 (men); N3 sleep (%), 8.6±7.2 (women), 6.6±6.7 (men) (23). PSG studies in cirrhosis are very few. Teodoro et al. investigated SDs in patients with cirrhosis;

they reported that the sleep duration decreased, sleep efficiency decreased, SL increased, and REM latency increased in such patients (4). In our study, pretransplant and 9-month posttransplant PSG results revealed that posttransplant TST and duration of all the sleep stages (REM and NREM [N1, N2, and N3]) increased relative to pretransplantation. SL and REM latency were found to be reduced. However, only the increase in S1 sleep and the decrease in SL were found to be statistically significant. Periodic limb movements per hour and AHI values were similar between the 2 groups.

EEG reflects postsynaptic activity of the pyramidal cells of the brain cortex that is extremely sensitive to the influence of toxic, metabolic, and pharmacological factors. In patients with HE, the basic rhythmic activity of the EEG progressively slows down, and the reactivity to eye opening reduces and finally disappears. The other component is "triphasic waves," which are not specific to this metabolic encephalopathy, and can be seen in moderate/severe HE. In this study, after LTx with the reversibility of bioelectric brain dysfunction, visual EEG performances significantly improved as in studies with spectral EEG (24, 25).

There are some limitations to this study. The major limitation is the small population size. PSG is an expensive and specialized method that is not practiced everywhere. Therefore, the number of patients included in this study was limited. Another limitation is that single-night PSG recordings were performed in this study. As PSG may be a first-night effect, some authors suggest two-night hospitalization for PSG. Adding a second-night PSG recording may reduce the adjustment process experienced by the patient on the first night. Another limitation was that spectral analysis of the EEG could not be performed. Spectral EEG assessment has been found to be more reliable than qualitative visual EEG reading in the diagnosis of overt and minimal HE, especially in the accurate detection of mild HE.

LTx improves the liver function, and cirrhosis complications are expected to disappear after transplantation. A small number of SD studies and data are available in this patient group. Ours is the first study to compare SDs by subjective and objective methods in pre and posttransplant patients. Posttransplant results revealed significant improvements in SDs at 9 months. Further studies with larger populations and longer follow-ups are required.

Ethics Committee Approval: Ethics committee approval was received for the study from the Ethics Committee of Yeni Yüzyıl University (21.07.2017/035).

Informed Consent: Written informed consent was obtained from all participants.

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