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Sleep Science

EDITORIAL

Letter from the president - XIV Brazilian sleep congress

The Brazilian Association of Sleep - (*Associação Brasileira de Sono* - ABS promotes, every two years, a meeting that brings together physicians from various specialties, researchers, technicians, dentists, biologists and psychologists, demonstrating the peculiar multidisciplinary of Sleep Sciences. Therefore, it is with great joy that I invite all the scientific community to XIV Brazilian Sleep Congress, which will take place on 21st to 24th November - 2013, in *Rio de Janeiro* - the Marvelous City - at Windsor Barra Hotel, right in the shore of Barra da Tijuca's beach.

This conference will be held at a time of particular relevance for Brazilian Sleep Medicine, which was finally considered by the Brazilian Medical Association (*Associação Médica Brasileira* - AMB) as a formal and official actuation area for four medical specialties: Neurology, Pulmonology, Otorhinolaryngology and Psychiatry. Also in this context, the Brazilian Association of Sleep Medicine (*Associação Brasileira de Medicina do Sono* - ABMS) was founded, with the purpose to bring together all the physicians interested in Sleep Medicine, as well as to expand our actuation fields to other medical specialties.

The world's spotlights are directed to *Rio de Janeiro*. We are on a moment in which every major event with international repercussion needs to come by us. We have recently received the visit and blessings of Pope Francis, during the World Youth Day. Also, we held the last Confederations Cup, which brought people from several nationalities to our city. Moreover, in a little while we will hold the next Soccer World Cup and the Olympics Games. It is in this context that we shall contextualize this next Brazilian Sleep Congress, a high quality scientific event among all those aforementioned.

The Scientific Committee is not measuring efforts in search of updated themes and speakers from Brazil and abroad, all of them reputed and with unequivocal qualification in both Sleep Medicine and Biology. Thus, I invite all those who are engaged in research to also submit their work and collaborate for the multiplication of knowledge in the area of sleep. In addition, important news will mark the event in 2013: simultaneously with the Brazilian Sleep Congress will also happen the I Congress of Sleep Dentistry and the II Luso-Brazilian Symposium of Sleep, which consolidates the partnership with our brothers overseas. Finally, we are working hard throughout this year in the updated version of the Consensus of Sleep Apnea and Insomnia, in order to make them available to all the participants in this meeting.

Despite the seriousness of the event, we cannot forget that we are in the Marvelous City, which is itself an invitation to natural relaxation and leisure. Enjoy this unique opportunity to socialize and see friends, appreciating the beauty that only *Rio de Janeiro* offers.

A friendly hug,

Andrea Bacelar,
President of the XIV Brazilian Congress of Sleep,
Vice President of ABS.

Sleep Science

LETTER TO THE EDITOR

Relevance of pre-clinical research on drug abuse and Sleep

A relevância da pesquisa pré-clínica sobre drogas de abuso e sono

Yone Gonçalves de Moura[1]

TO THE EDITOR:

The article entitled "Sleep and drugs of abuse: overview of preclinical research and new global trends"[1], published by Polesel et al. in the last issue of Sleep Science brings important data regarding the relationship between drug abuse. It deals with two themes that are intimately related, presenting interesting pre-clinical results which increase the comprehension on this relationship, as well as motivate more studies on the field.

This review presents alcohol as the most accessed substance in pre-clinical studies about sleep and drug abuse. This data corroborates the most important epidemiological studies in Brazil, which demonstrate alcohol as the most prevalent substance in general population. Noto et al.[2] says that the study of alcohol abuse is a major public health concern, as this substance is one of the main causes of drug-related hospitalization. This fact can also be observed in previous epidemiological studies. In the II Brazilian Household Survey on Psychotropic Drugs, the the prevalence of alcohol consumption in life was 74.6%[3]; in the VI Brazilian Survey on Drug Use among Students, the same consumption was about 60.5%[4]; and in the Drug Abuse Survey among Undergraduate Students was 86.2%[5].

The aforementioned study raises two possible explanations for the higher number of pre-clinical research involving sleep and alcohol. The first explanation draws upon the depressive effects of alcohol, which has influence over sleep architecture. This factor would be the main factor explaining such production in pre-clinical research. The second explanation, the legality of alcohol consumption, which is present in several countries, has already been demonstrated as a main concern in epidemiological studies. These concerns are not only directed to adults, but also to adolescents, which are starting to use alcohol and other drugs earlier, in a vital cycle of pleasure seeking[6]. When we consider that adolescents are in physical and emotional self-construction, this becomes a valuable data regarding to public health. These pre-clinical studies bring fundamental information about alcohol and sleep, as these adolescents are day after day more requested by the modern lifestyle requirements.

Accordingly, this article brings clarifying points for researchers in the field of drug abuse, corroborating previous epidemiological studies and instigating more efforts on the relationship between drugs abuse and sleep. As the article says, several studies have already demonstrated that sleeping is an important factor for a healthy life, but that can also lead to important public health problems. The forthcoming studies about sleep and drug abuse deserve attention, as they will probably be able to develop public policies and prevention strategies to be applied in both fields.

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Sleep Science

ORIGINAL ARTICLE

Arousals and macrostructure of sleep: importance of NREM stage 2 reconsidered

Despertar e macroestruturas do sono: importância de reconsiderar o estágio NREM

Zakevicius Martynas[1], Liesiene Vanda[2], Griksiene Ramune[1], Masaitiene Raminta[3], Ruksenas Osvaldas[1]

ABSTRACT

Objectives: The sense of rest after sleep and its relation to various sleep parameters is still a debatable issue. The purpose of the present study was to analyse sleep fragmentation by scoring various arousals (microarousals (MA), vegetative (VA) and behavioural (BA) arousals) in all sleep stages and to evaluate their relation with subjective sleep quality without paying attention to the type of insomnia. **Methods:** The overnight sleep cycles of 60 subjects were analyzed according to their stage composition and arousals. Arousal indices (AI) were calculated for all types of arousals in all sleep stages and sleep cycles. The sleep quality was quantified using the Pittsburgh sleep quality index (PSQI). **Results:** AI differences between sleep cycles were not statistically significant. MAI value in total sleep time (TST) - 5.8 ± SD 4.1 - was the highest among all the three arousal types. Differences between AI in most sleep stages were statistically significant for all types of arousals. This suggests that human sleep development within a single sleep cycle is more important for the sleep quality than the changes between different sleep cycles. The highest AI scores for the three types of arousals were found in NREM stage 2. The strongest and significant correlation was between PSQI and MAI (r = 0.42; p = 0 .001). **Conclusion:** The density of microarousals is important for the subjective sleep quality. The highest values of MAI and other arousal types are found in NREM stage 2. The importance of this stage might be higher than thought before and especially in initial sleep cycles.

Keywords: sleep, sleep arousals disorders, sleep stages.

RESUMO

Objetivos: O sentido de descanso após o sono e sua relação com vários parâmetros do sono ainda é uma questão discutível. O objetivo do presente estudo foi analisar a fragmentação do sono, marcando vários despertares (microdespertares (MA), vegetativas (VA) e comportamentais (BA) despertares) em todas as fases do sono e avaliar sua relação com a qualidade subjetiva do sono, sem prestar atenção ao tipo de insônia. **Métodos:** Os ciclos de sono durante a noite de 60 indivíduos foram analisados de acordo com a sua composição palco e despertares. Índices de excitação (AI) foram calculados para todos os tipos de despertares em todas as fases do sono e os ciclos do sono. A qualidade do sono foi quantificada através do índice de qualidade do sono de Pittsburgh (PSQI). **Resultados:** Diferenças entre AI ciclos de sono não foram estatisticamente significativas. MAI valor no tempo total de sono (TST) - 5,8 ± SD 4.1 - foi o maior entre todos os três tipos de excitação. Diferenças entre AI na maioria dos estágios do sono foram estatisticamente significantes para todos os tipos de despertares. Isto sugere que o desenvolvimento de sono humano dentro de um único ciclo do sono é mais importante para a qualidade do sono do que as variações entre diferentes ciclos de sono. Os maiores escores de IA para os três tipos de despertares foram encontrados em fase NREM 2. A correlação mais forte e significativa foi entre PSQI e MAI (r = 0,42, p = 0, 001). **Conclusão:** A densidade de microdespertares é importante para a qualidade subjectiva do sono. Os maiores valores de MAI e outros tipos de excitação são encontradas em fase NREM 2. A importância desta fase pode ser maior do que se pensava antes e, especialmente, nos ciclos iniciais do sono.

Descritores: fases do sono, sono, transtornos do despertar do sono.

INTRODUCTION

The overnight course of sleep is not a simple linear process, and it exhibits a very complex behavior which involves various areas of the central nervous system at different levels and at different times[1]. The daily shifts from the wake state to NREM and REM sleep are under the control of interconnected processes, including the circadian timing of sleep onset, the homeostatic balance between wakefulness and sleep and the ultradian interaction between NREM and REM sleep[2].

More recently, and especially to explain the clinical consequences of sleep disorders, the three processes of sleep regulation - circadian, homeostatic and ultradian - have been integrated by the definition of the arousal system[3]. Arousals are transient episodes of cerebral activation during sleep which involves massively the cortex regulated by the interplay between cortical and subcortical neurons[3,4]. Most authors consider arousals as a transient cortical activation in response to sleep disruptive events[5-7], but there are other studies indicating that

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arousals punctuate both REM and NREM sleep even in the absence of detectable disturbing stimuli[8,9].

On the one hand, there are debates still going on about the nature and role of arousals in sleep, and on the other hand, there is a question about their role for the sleeper him/herself - how his/her sleep quality is affected by them. There are various studies trying to evaluate a person's sense of rest after the sleep in the morning, but researchers still disagree about what determines the sense of rest after the sleep[10]. There are findings which showed that the subjective satisfaction after the sleep is not dependent on the overall sleep length[11]. It was assumed that the amount of delta sleep is very important in sleep structure, but it wasn't exactly confirmed and even people with sufficient amounts of deep sleep might feel unrested in the morning[5]. A lot of attention is recently paid to the sleep integrity and the role of sleep fragmentation, which is characteristic of primary insomnia and could have an effect on the sleep's restorative function[12,13].

The aim of the present study was to analyze sleep fragmentation by scoring different type arousals in all sleep stages and cycles and to evaluate their relationship with the subjective sense of rest after the sleep without paying attention to the type of insomnia.

MATERIAL AND METHODS

Subjects

The data analyzed in this study were collected from the all night polysomnographic (PSG) recordings of 60 subjects (30 men and 30 women) aged between 36 and 55 years (mean 46 ± SD 5.6 years). Subjects were recruited from clinical patients of the Sleep disorders laboratory at Vilnius Sapiegos hospital in Vilnius. All subjects were diagnosed with various sleep disorders. The only exclusion criteria were sleep apneas and heavy snoring problems. They had all night PSG study performed in the sleep disorders laboratory and woke up in the morning at their usual time. Before the study, patients had consultations with the doctor, filled out necessary questionnaires and provided written informed consents. All clinical experiments conformed to the principles outlined by the Declaration of Helsinki.

Arousal scoring

A monopolar derivation (C3-A2 or C4-A1) was used to score sleep stages[14] and arousals. Arousals were scored and arousal indices (AI) (the number of arousals per hour of sleep) were calculated in three major groups to represent different levels of cortical and somatovegetative activations:

- Behavioural arousal (BA): reported in the Rechtshaffen and Kales manual[14] as a movement arousal described as any increase in electromyographic activity that is accompanied by a change in any other EEG channel.
- Micro (cortical) arousal (MA): defined by the American sleep disorders association (ASDA) committee in 1992 as EEG arousal and characterized by transient desynchronized EEG patterns interrupting sleep. It reflects a brief awakening of the cerebral cortex regardless of any concomitant participation of the autonomic system or behavioral components[3].
- Vegetative (autonomic) arousal (VA): identified when vegetative activation is associated with a transient EEG pattern different from a conventional ASDA arousal[15,16].

The Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI)[17] was developed to measure sleep quality during the previous month and to discriminate between good and poor sleepers. The PSQI has been used to measure sleep quality among truck drivers[18], to test the effects of a drug on sleep quality in a randomized placebo controlled trial[19] and others.

Sleep quality is a complex phenomenon that involves several dimensions, each of which is covered by the PSQI. The covered domains include Subjective Sleep Quality, Sleep Latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disturbances, Use of Sleep Medications, and Daytime Dysfunction. The PSQI is designed to assess sleep quality during the past month and contains 19 self-rated questions and 5 questions rated by a bed partner or roommate (only the self-rated items are used in scoring the scale). Seven component scores that correspond to the domains listed previously are calculated and summed into a global score[17]. A score of 5 and more indicates poor sleep quality; the higher the score, the worse the sleep quality. Component scores range from 0 to 3 and global scores range from 0 to 21.

Protocol

All patients who took part in the study were patients of the Sleep disorders laboratory in Vilnius Sapiegos hospital. As part of their standard clinical assessment they completed the PSQI at their initial patient consultation and a clinical history was taken. An overnight sleep study was then performed using the electrophysiological recording equipment (SleepLab Applications from VIASYS® Respiratory Care Inc., Viasys Healthcare GmbH, Hoechberg, Germany) to measure 4 EEG leads (C3, C4, P3, P4 referenced to linked ears), an electrooculogram (EOG), an electromyogram (EMG), and an electrocardiogram (ECG). Also arterial oxygen saturation (SaO_2) was determined, respiration was monitored with thermistors and thoracic movements, and tibialis electromyographic activity was recorded using surface electrodes placed on the right and left legs. The sleep laboratory was equipped with video and sound recording devices for additional monitoring of body movements and sounds. All equipment was time synchronized.

Subjects went to bed at their usual time and were asked to refrain from drinking beverages containing caffeine or alcohol in the previous afternoon and evening hours. In the morning they also awakened at their usual time.

Sleep stages were visually scored according to standard criteria[14] using 30-second epochs, with the investigator blind to subject and experimental conditions. Standard sleep parameters were computed over the complete sleep time period, and all recordings were analyzed for sleep staging and arousal scoring with the Matrix Sleep Analysis SleepLab® for Windows (version 1.70.0.3) software package.

Statistics and data evaluation

All PSG recordings were analyzed and conventional PSG measures that were obtained from that analysis were: total sleep time (TST), time in bed (TIB), sleep efficiency (SE), sleep latency (SL), wake after sleep onset (WASO), total duration and percentages of non-rapid eye movement sleep (NREM) stage 1 (N1), stage 2 (N2), stage 3 (N3) and stage 4 (N4), and rapid eye movement sleep (REM). Stages 1 and 2 together are referred to as light sleep (LS), Stages 3 and 4 together are referred to as deep sleep (DS).

Each PSG recording was subdivided into sleep cycles. The first sleep cycle started at sleep onset and the following sleep cycle started with the first epoch of NREM sleep after a completed REM sleep episode. All sleep cycles ended with the last epoch of the included REM sleep episode. According to adopted procedures[20,21], a REM sleep period was considered completed when the duration of the NREM stage following the last epoch scored as stage REM exceeded 15 min. The sleep time preceding the final awakening not completed by REM sleep episode was not included in the cycle calculation. For each sleep cycle the total duration, stage composition and percentages were analyzed. Arousal indices (AI) were quantified in TST, NREM sleep and in each of NREM sleep stages, REM sleep, separately and in every sleep cycle. Before every calculation subjects with calculated parameters exceeding ± 3SD were excluded from data analysis, therefore the number of analysed subjects (N) differs in different calculations.

Examination of the data and the Kolmogorov-Smirnov and Chi-square tests for normality suggested that variables were normally distributed. Pearson correlation thus was used to examine the relationships between each of the arousal indices and PSQI in all sleep stages and sleep cycles. The PSG data from different sleep cycles was analyzed and compared by a factorial ANOVA followed by a post-hoc Bonferroni test. All the statistics were calculated using the STATISTICA v 8.0 software (StatSoft Inc., USA).

RESULTS

General sleep parameters

Total sleep time in general group (N = 55) was 418 min. Sleep efficiency was 85%, which was less than reported 94% in the study by Terzano et al. with normal healthy subjects[6].

In 22 subjects, sleep was organized in four completed sleep cycles, in 27 subjects - in five, and only 4 patients had six sleep cycles. Subjects with parameters exceeding ± 3SD were excluded from the data analysis. Table 1 reports the structural parameters of five sleep cycles derived from 24 subjects, four sleep cycles derived from 40 subjects, three sleep cycles from 41 and two sleep cycles from 44 subjects. The sixth sleep cycle was not taken into consideration as it was found only in two subjects.

The average duration of the sleep cycle was 90 min. The third sleep cycle was the longest and the fifth sleep cycle was the shortest, but the length of the fifth sleep cycle did not differ significantly (Table 1). The amount of deep sleep declined from the first to the last sleep cycle (in N3 $p < 0.001$, F = 1.717 and in N4 $p < 0.05$, F = 6.439) with especially sharp reduction between the second and the third sleep cycles. The duration of light sleep was lower in the first two sleep cycles becoming more stable in the third and fourth sleep cycles and rising in the fifth. Differences of N2 durations in different sleep cycles were significant ($p < 0.001$, F = 1.342) and those of N1 were not. REM sleep duration increased from the first to the last sleep cycle ($p < 0.05$, F = 3.293) (Table 1 and Figure 1).

Arousals

All AI rose from the first to the second sleep cycle during the night and then varied, but there were no significant differences between AIs in different sleep cycles. MAI in TST - 5.8 ± SD 4.1 - was the highest among all the three arousal types. BAI in TST was 4.8 ± SD 2.7 and VAI in TST was 3.0 ± SD 2.4 (Table 2).

Looking from sleep staging perspective, the situation with AI is different. Differences between AIs in most sleep stages are significant for all types of arousals. The highest AI scores are found in NREM stage 2 and the lowest in NREM stage 4. AI values rise from N1 to N2 and then decline as sleep gets deeper. AI values in REM are in between N2 and N3 values. MAI values are higher than BAI and VAI values in the most of stages (Table 3).

Subjective sleep quality

Average Pittsburgh Sleep quality index (PSQI) for all subjects was 13.0 ± SD 4.4. This is normal in our case, because all the subjects have been diagnosed with some sleep disorders.

The correlation between conventional sleep staging parameters (stage duration, % from TIB, % from TST) and PSQI gradually progresses from light sleep into deep sleep (Figure 2). Significant correlations for all the three parameters were only between wake (W) duration and PSQI (r = 0.3; $p < 0.05$) and between N4 duration and PSQI (r = -0.3; $p < 0.05$) (Figure 2).

The strongest and significant correlation was between PSQI and MAI (r = 0.42; $p = 0.001$). There was no significant correlation between PSQI and other types of AI. It could be that for the subjective sense of sleep quality not just one particular type of arousals might be important, but the combination of all of them. Grouped arousal indices (e.g. MAI + BAI) had stronger significant correlations with PSQI (r = 0.5; $p < 0.0001$) than single type arousals.

No significant AI differences between sleep cycles (Table 2) and significant AI differences between sleep stages (Table 3) suggested that the sleep stage is a more important factor for AI than the sleep cycle. So we calculated three types of AI for all sleep stages in every sleep cycle and analysed them. Factorial ANOVA showed that the sleep stage ($F(4, 3117) = 20.825$; $p < 0.0001$; $\eta^2 = 0.026$), but not the sleep cycle ($F(4, 3117) = 0.676$; $p = 0.6$; $\eta^2 = 0.001$) is a significant factor for AI value. The arousal type was also a significant factor for AI ($F(2, 3117) = 13.290$; $p < 0.00001$; $\eta^2 = 0.008$). For factorial ANOVA test, AI was a dependent variable and the sleep cycle (I-V), the stage (N1-N4, REM), and the arousal type (MA vs. VA vs. BA) were categorical predictors (factors).

Table 1. Stage duration in sleep cycles.

	I cycle	II cycle	III cycle	IV cycle	V cycle	*p*	F	Significantly differing sleep cycles
Number of subjects	44	44	41	40	24			
TST (min)	86.4 ± 21.8	92.3 ± 19.6	94.8 ± 30.0	92.6 ± 18.2	83.5 ± 24.3	n. s.		
WASO (min)	6.4 ± 8.1	4.0 ± 6.7	6.9 ± 9.6	4.6 ± 8.7	4.9 ± 8.2	n. s.		
N1 (min)	11.5 ± 8.6	6.6 ± 7.2	9.5 ± 13.5	9.1 ± 9.1	12.5 ± 2.3	n. s.		
N2 (min)	23.0 ± 11.4	29.7 ± 12.9	36.8 ± 12.3	37.1 ± 13.2	34.6 ± 14.3	< 0.001	1.342	3 > 1; 4 > 1; 5 > 1
N3 (min)	23.9 ± 12.7	23.9 ± 12.7	18.9 ± 15.8	11.3 ± 9.7	4.5 ± 6.1	< 0.001	1.717	1 > 4; 1 > 5; 2 > 4; 2 > 5; 3 > 5
N4 (min)	12.8 ± 12.5	10.8 ± 11.1	4.1 ± 6.9	3.8 ± 7.6	1.4 ± 4.9	< 0.05	6.439	1 > 5;
NREM (min)	71.1 ± 16.5	70.9 ± 17.2	69.3 ± 21.3	61.3 ± 15.4	53.0 ± 16.4	n. s.		
REM (min)	8.8 ± 8.0	17.4 ± 12.6	18.7 ± 13.4	26.6 ± 15.0	25.6 ± 14.6	< 0.05	3.293	3 > 1; 4 > 1; 5 > 1;

TST: Total sleep time; WASO: Wake after sleep onset; N1, N2, N3, N4: Stages 1, 2, 3, 4; NREM: Non-rapid eye movement sleep; REM: Rapid eye movement sleep; *p*: Significance of inter cycle differences; F: F-ratio variance; Average ± SD.

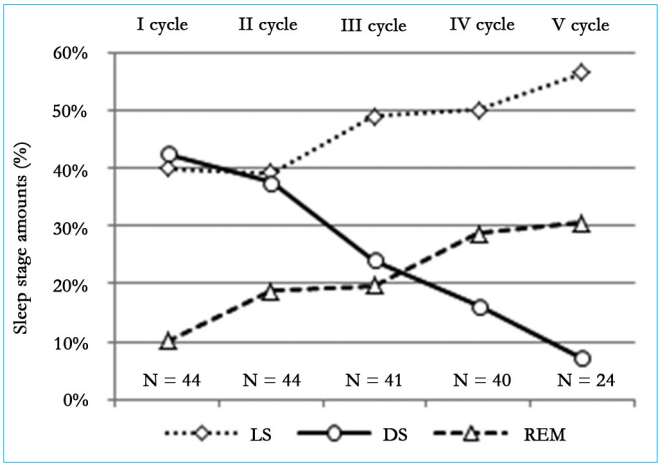

Figure 1. Average proportions of light sleep (LS), deep sleep (DS) and REM sleep in different sleep cycles; N: Number of subjects.

Table 2. Arousal indices in sleep cycles.

	I cycle	II cycle	III cycle	IV cycle	V cycle
Number of subjects	46	45	42	40	24
BAI	4.7 ± 4.1	5.3 ± 4.4	3.9 ± 2.7	3.7 ± 3.0	4.2 ± 3.0
MAI	4.4 ± 4.0	5.2 ± 5.5	5.1 ± 4.2	4.1 ± 3.3	6.9 ± 5.7
VAI	1.6 ± 1.7	3.2 ± 3.3	2.6 ± 2.7	2.9 ± 2.8	3.3 ± 3.1

BAI: Behavioural arousal index; MAI: Microarousal index; VAI: Vegetative arousal index; Average ± SD.

Correlations between the amount of light sleep and deep sleep in sleep cycles with PSQI were not significant. This relation in case of deep sleep from negative (r = -0.20) becomes neutral (r = 0.04) going from the first to the fifth sleep cycle and in case of light sleep - from positive (r = 0.23) to more neutral (r = 0.12). The correlation between the amount of REM sleep and PSQI values varies a lot from one sleep cycle to another over the night (Figure 3).

The correlation between different types of AIs and PSQIs changes during the night. MAI correlation rises during the night while BAI and VAI decrease (Figure 4). Statistically significant correlation with PSQI showed only BAI (r = -0.34; $p = 0.02$) and VAI (r = -0.33; $p = 0.03$) in the fifth sleep cycle.

AI's dynamics during the night is closely related to the duration of sleep stages in each sleep cycle.

DISCUSSION

The present study was undertaken to analyse sleep structure and fragmentation in terms of arousals (behavioural, micro and vegetative) and their distribution during the night and to evaluate if there is any relation with the subjective sense of rest after the sleep without paying attention to the type of insomnia.

Stage-dependent EEG modifications, the cyclic alternation between NREM and REM sleep, which develops in four to six 90-min ultradian cycles, the decline of deep sleep and the increase of light sleep during the night are the most relevant contributions supplied by the conventional criteria to understand the structure of sleep[22-24]. Our study showed that this holds true also in subjects with sleep disorders. The composition of the single sleep cycle varies in the course of the night - the period length of deep sleep decreases from the first to the last sleep cycle and at the same time light sleep and REM sleep undergo a progressive increase (Figure 1). But the question to us was how all this relates to the person's sense of rest in the morning.

The importance of deep sleep for the subjective sense of rest after the sleep was shown as a significant negative correlation between Pittsburgh sleep quality index (PSQI) and deep sleep (N4) amount (r = -0.3; $p < 0.05$) (Figure 2). This was in accordance with similar previous studies by other authors [5,25]. And this is not a static effect. During the course of night - going from the first to the last sleep cycle - this relation gets weaker, indicating the importance of initial sleep cycles to the overall sleep quality sense (Figure 3).

From all the three arousal types that we have studied MAI in TST showed the highest correlation with PSQI (r = 0.42; $p = 0.001$). VAI in TST showed negative correlation with PSQI and this means that the more vegetative arousals patient has, the better his sleep quality is. That was unexpected, but it could be that internally generated vegetative arousals to some extent play an important role in sleep regulation and express not negative sleep disturbances, but maintenance of internal body functions instead[9].

Table 3. Arousal indices in sleep stages.

	N1	N2	N3	N4	REM	*p*	F	Significantly differing sleep stages
Number of subjects	45	45	45	45	45			
BAI	11.7 ± 9.3	19.0 ± 14.0	3.6 ± 4.0	0.7 ± 1.2	9.3 ± 9.4	< 0.05	2.275	1 > 3; 1 > 4; 2 > 1; 2 > 3; 2 > 4; 2 > REM; REM > 4
MAI	11.1 ± 11.0	25.1 ± 21.3	4.1 ± 5.0	0.2 ± 0.5	12.9 ± 11.1	< 0.0001	3.702	1 > 4; 2 > 1; 2 > 3; 2 > 4; 2 > REM; REM > 3; REM > 4
VAI	6.1 ± 6.7	15.8 ± 15.6	2.5 ± 3.6	0.3 ± 0.6	7.3 ± 6.9	< 0.01	5.369	2 > 1; 2 > 3; 2 > 4; 2 > REM

BAI: Behavioural arousal index; MAI: Microarousal index; VAI: Vegetative arousal index; N1, N2, N3, N4: Stages 1, 2, 3, 4 of non-rapid eye movement sleep; REM: Rapid eye movement sleep; *p*: Significance of inter cycle differences; F: F-ratio variance; Average ± SD.

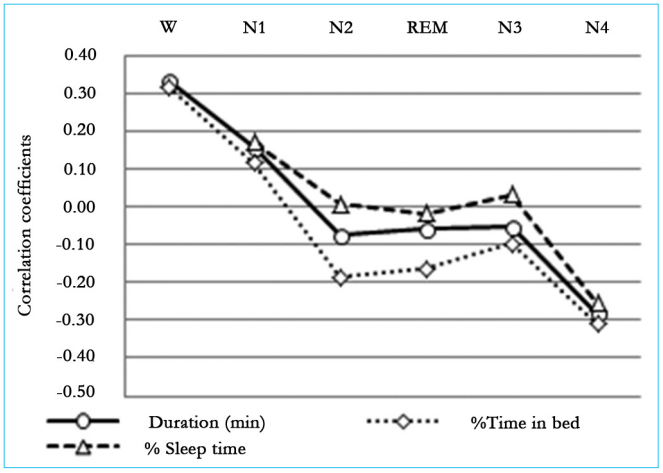

Figure 2. Pittsburgh sleep quality index correlations with conventional sleep parameters (N = 51). W: Wake; N1, N2, N3, N4: Stages 1, 2, 3, 4 of NREM (non-rapid eye movement sleep); REM: Rapid eye movement sleep.

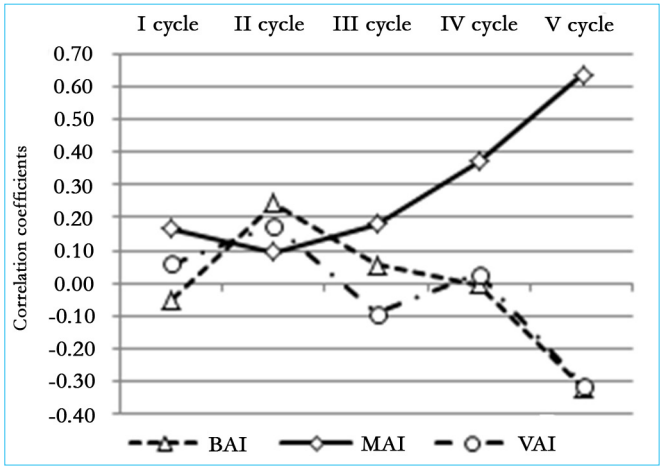

Figure 4. Pittsburgh sleep quality index correlations with different type arousals in sleep cycles (N = 46). BAI: Behavioural arousal index; MAI: Microarousal index; VAI: Vegetative arousal index.

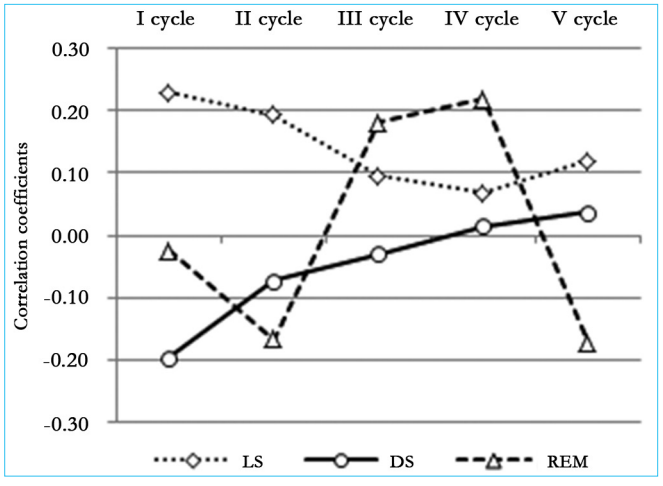

Figure 3. Pittsburgh sleep quality index correlations with light sleep and deep sleep duration in different sleep cycles (N = 44). LS: Light sleep; DS: Deep sleep; REM: Rapid eye movement.

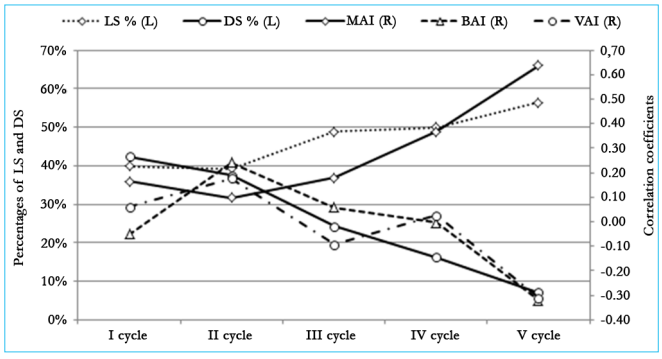

Figure 5. Pittsburgh sleep quality index correlations with different type arousals in sleep cycles (N = 46). LS %: Percentage of light sleep; DS %: Percentage of deep sleep; BAI: Behavioural arousal index; MAI: Microarousal index; VAI: Vegetative arousal index; L: Left hand side axis; R: Right hand side axis.

AIs dynamics during the night is closely related to the duration of sleep stages in each sleep cycle. MAI correlations with PSQI increase from cycle to cycle, but it is not significant and is mainly related to increasing proportion of light sleep in each sleep cycle and especially N2. Correlations between BAI, VAI and PSQI become more negative over the night in parallel with decreasing amount of deep sleep in each sleep cycle (Figure 5). This negative trend is similar to the negative correlations between PSQI and VAI in TST. That could be related to the maintenance and preparation of internal body functions before the morning time awakening.

Not significant AI differences between sleep cycles (Table 2) and significant AI differences between sleep stages (Table 3) suggested that developments of human sleep within the single sleep cycle are more important for the sleep quality than the changes between sleep cycles. Factorial ANOVA confirmed that the sleep stage and the arousal type were significant factors for the AI values, whereas the sleep cycle was not (see above in *Subjective sleep quality*).

The highest AI values were found in N2 stage and MAI in this stage was higher than the other two AIs (Table 3). On this basis, we suggest that not only the sleep stage proportions (the amount of deep sleep) are important to feel good after the sleep, but the microstructure of each stage, and especially N2, might be significant for that also.

What is happening during N2 in the human body that we could think of its importance? The average cerebral metabolism and blood flow begin to decrease in N2 compared to wakefulness[26,27]. Comparing the influence of high (34-37ºC) and low (21ºC) ambient temperatures on sleep, Haskell et al. pointed out that the durations of wakefulness and N1 sleep increased in cold exposure whereas the duration of N2 sleep decreased[28]. They concluded that cold was more disruptive to sleep than heat. A similar observation has been reported by Palca et al.[29]. For naked subjects exposed for five consecutive nights at 21oC cold exposure increased wakefulness and decreased N2 sleep without any change in other sleep stages. That shows that sleep disruption might be expressed as the reduction in N2 sleep.

The increase in slow wave activity during NREM sleep is associated with low adrenocorticotropic activity and low sympathetic activity, whereas N2 clearly reveals its hormonal and autonomic duality, depending on whether it prepares for deep sleep or REM sleep[30]. It could be that sleep disorders might result from an alteration of the autonomic nervous system activity, or from inadequate coupling between endocrine, autonomic, and EEG ultradian rhythms[31].

In healthy nocturnal young subjects, oral administration of exogenous melatonin before going to bed increased N2 amount significantly, with slight hypothermic action[32]. The effect of a high melatonin dose (80 mg p.o.), when tested in subjects with insomnia induced by exposure to recorded traffic noise, was a reduction of sleep latency and of the number of awakening episodes and the increase of N2 sleep and sleep efficiency[33]. Administration of 3-mg dose of melatonin during 14 nights to elderly patients with chronic primary insomnia brought about a significant reduction in WASO while TST and SE increased, with an increase of N2 stage[34]. It turns out that pharmaceutical improvement of sleep influences mostly N2 stage.

Individuals who learn a new task have a significantly higher density of sleep spindles, which is one of the markers of N2 stage, than those in a control group[35] and the improvement of performance after a period of sleep is correlated with the percentage of N2 sleep[36].

From all these findings we can see that N2 stage is associated and correlated with good sleep quality and sleep disruptive conditions make the most impact on N2 stage also. That and recent findings about sleep mechanism disruptions and its possible connection with some pathologies (from cognitive to metabolic defects)[37,38] raise new thoughts. Stabilization of sleep and especially in NREM stage 2 might help to reduce symptoms of these pathologies and give way for other specialists to intervene more effectively with their therapy. Moreover, the importance of this stage gets new meaning in the light with emerging concepts of sleep-wake cycle regulation and transition from NREM to REM sleep and vice versa, which usually is happening through NREM stage 2[39,40].

In summary, it can be concluded that microarousal density is important for the subjective sense of rest after the sleep. The highest values of MAI and other arousal types are found in NREM stage 2. That is why we point out that the importance of this stage might be higher than anticipated and especially in initial sleep cycles. It is well known that during N2 essential changes in thalamo-cortical circuits take place andtemporary deafferentation of sensory influx to cortex occurs. It is assumed that this creates special conditions for cortical restorative processes. The stability of N2 defines how deep sleep which is responsible for the metabolic restoration unrolls. If during this stage everything goes well in the brain and sleep is undisrupted, then deep sleep plays its role and sleep quality is good, but if something goes wrong in this stage, e.g. sleep is fragmented by microarousals, and then sleep quality becomes poorer.

There are a few limitations in our study that we would like to point out. First off all - age. Subjects' age in this study varied from 35 to 55 years and this might have had some impact on the study results. It would be useful to collect a larger group of subjects in a narrower age range. The second is the type of sleep disorders. We wanted to see if there is any relation between the sleep microstructure in terms of arousals and the subjective sense of rest after the sleep without paying attention to the type of a sleep disorder. But a different type of a sleep disorder might have variable effects on the sleep microstructure and then on the sense of rest.

Even though we analysed the data from patients who had various sleep disorders, we think that general concept that sleep fragmentation has a negative impact on sleeper's sense of rest after the sleep applies for both people with and without sleep disorders.

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Sleep Science

ORIGINAL ARTICLE

Sleep disturbances complaints in stroke: implications for sleep medicine

Queixas de distúrbios do sono no acidente vascular cerebral: implicações para a medicina do sono

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ABSTRACT

Objectives: The aim of this study was to evaluate stroke patients' sleep quality and its relationship with sleep disturbances complaints. **Methods:** A total of 70 subjects, 40 patients (57 ± 7 years) and 30 healthy controls (52 ± 6 years), assessed by the Pittsburg Sleep Quality Index (PSQI) took part in the study. Data analysis was realized by ANCOVA and multiple linear regression. **Results:** Significant differences in average PSQI were found between the groups (patients: 6.3 ± 3.5; healthy: 3.9 ± 2.2; $p = 0.002$). Regression analysis showed that the strongest predictor of sleep quality was compromised sleep efficiency (R^2 adjusted = 0.78) which may indicate less deep sleep can be compensated with increased daytime dysfunction, latency and sleep duration. **Conclusions:** We suggest that complaints of poor sleep quality be priority during clinical diagnosis.

Keywords: homeostasis, nervous system diseases, sleep disorders, stroke.

RESUMO

Objetivo: O objetivo deste estudo foi avaliar a qualidade do sono de pacientes com AVC e sua relação com as queixas de distúrbios do sono. **Métodos:** Participaram 70 indivíduos, 40 pacientes (57 ± 7 anos) e 30 controles saudáveis (52 ± 6 anos), avaliados pelo Índice de Qualidade de Sono de Pittsburg (PSQI). Para a análise, foi usada a ANCOVA e regressão linear múltipla. **Resultados:** Foi encontrada diferença significativa na média do PSQI entre os grupos (pacientes: 6,3 ± 3,5; saudáveis: 3,9 ± 2,2, $p = 0,002$). A regressão mostrou que o mais forte preditor da qualidade do sono foi a eficiência do sono (R^2 Ajustado = 0,78), o que pode indicar que a queixa da falta de sono profundo pode ser compensada com o aumento de disfunção diurna, latência e duração do sono. **Conclusões:** Sugerimos que as queixas de má qualidade do sono sejam prioridade durante o diagnóstico clínico.

Descritores: acidente vascular cerebral, doenças do sistema nervoso, homeostase, transtornos do sono.

INTRODUCTION

Stroke is defined as an acute neurological deficit lasting for more than 24 hours. It is caused by a cerebral blood flow anomaly resulting in signs and symptoms associated with compromised focal brain areas. The clinical picture can include sensory-motor dysfunctions, tonus alterations, posture control and equilibrium disturbances as well as cognitive dysfunctions[1].

Sleep disturbances bring about cognitive deficits, diminishing certain capabilities such as attention span, spatial and temporal orientation, and memory efficiency. They also compromise social and psychological function[2]. Thus, the acknowledgement of the possible occurrence of sleep related problems, directed toward stroke patient reports and complaints, seems to be an important component of the therapeutic, diagnostic and clinical approach adopted. For example, the rehabilitation process initiated at the onset of the disease can be continuous and prolonged in many cases. Poor sleep quality can compromise this process.

Quality of sleep is a difficult variable to define and measure in an objective manner. Alternatively, self-report methods such as sleep questionnaires provide a measurement of sleep quality experienced by the patient, while considering both the quantitative and qualitative aspects. These subjective methods are easily managed, inexpensive and can be widely applied in both research and clinical practice[3]. The Pittsburgh Sleep Quality Index (PSQI) is a questionnaire that has been widely used to measure sleep quality and components from pattern areas generally focused on by clinics when patients report sleeping problems[4].

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The greater prevalence of patients with sleep disturbances after stroke suggests an association between this pathology and sleeping problems. Many studies in the literature have given more attention to objective evaluation of sleep through polysomnographic patterns, considering mainly the acute phase of recovery[5,6]. In these studies the relationship between sleeping problem complaints and quality of sleep was not considered relevant, nor the question of which sleep regulation mechanisms could be affected.

Foley et al.[7] evaluated the association between sleeping problems and chronic illnesses in the elderly. They concluded that stroke is associated with the presence of one or more sleeping problems such as difficulty falling and staying asleep as well as daytime sleepiness. Müller et al.[6] also found that stroke patients woke more often after falling asleep and had less sleep efficiency than those without the disorder. Vock et al.[8], who evaluated post ischemic stroke patients, also established a greater frequency of post-stroke sleep anomalies.

Thus, the aim of this study was to evaluate subjective quality of nocturnal sleep in hemispheric stroke patients and its relationship with sleep disturbances complaints.

MATERIAL AND METHODS

Subjects

The sample was composed of 70 subjects, including a group of 40 patients with diagnosis of unilateral stroke enrolled at physical therapy services in the city of *Natal*/RN who were compared to a group of 30 healthy employees of the Federal University of *Rio Grande do Norte*. The group of patients was composed of 27 men and 13 women, aged between 45 and 65 years (57 ± 7 years), lesion time between 1 and 36 months (11 ± 9 months), with 24 and 16 patients presenting with impaired right and left cerebral hemisphere, respectively. The group of healthy individuals was composed of 15 men and 15 women, aged between 45 and 64 years (52 ± 6 years). Schooling level varied between grade 6 and grade 11.

The exclusion criteria adopted for the patients were: recurrent cerebral lesion, serious cognitive disorders, aphasia and the use of tranquilizers, antidepressants or neuroleptics. For the controls, individuals with cognitive disorders, night workers or those who had taken a recent transmeridian trip were excluded. The recruitment of the participants was carried through personal contact in the institutions where the research was executed and the participation of them was voluntary.

Procedures

This study was conducted in accordance with the Declaration of Helsinkiand approved by Research Ethics Committee of the Federal University of *Rio Grande do Norte*. The participants were informed of the research procedure and asked to sign a voluntary consent form.

The patients were interviewed and provided the following information: identification, results of computerized tomography, history of the disease, risk factors present, medication used and lesion time. The Cumulative Illness Rating Scale (CIRS), an assessment scale of comorbidities, was used with the healthy individuals. This scale consists of a standardized clinical evaluation that investigates the overall health data of the individual in six organic systems, with scores ranging from 0 to 4, to ensure the current healthy status of the individual[9]. To determine the degree of neurological impairment of the patients, we used the National Institute of Health Stroke Scale (NIHSS)[10]. The scale is composed of 11 items that assess awareness level, eye movements, visual field, facial movements, motor function and upper and lower limb ataxia, as well as sensitivity, language, presence of disarthria and visual-spatial neglect. The total score, ranging from 0 to 42 points, is the sum of the points of each item, in which higher scores indicate greater neurological impairment. A score between 0-6 indicated little damage, between 7-16 moderate damage, and between 17-30 severe damage. The subjective sleep evaluation of the participants was determined by applying the PSQI. It consists of 19 questions related to the previous month's sleeping habits, and is divided into 7 components: sleep quality, sleep latency (time needed to fall asleep), sleep duration (hours of sleep per night), sleep efficiency (total sleep time divided by time spent in bed), sleep disturbances (waking in the middle of the night or very early), use of sleeping medication and daytime dysfunction (difficulty staying awake). The sum of the 7 components varied between 0 and 21, a score equal and greater than 5 implying poor sleep quality[4]. The individuals who reported sleep problems were questioned as to the time frame of the problem in order to compare it with post-lesion time. This comparison confirmed whether the problem occurred before or after the stroke.

Statistical analysis

The data was analyzed using the SPSS 14.0 program (*Statistical Package for the Social Science*) at a significance level of 5%. Prior to analysis, the data were checked for normality using the Kolmogorov-Smirnov test. The non-paired Student's t-test was used to determine the difference between the patient group and the healthy group as to age and schooling. ANCOVA was used to determine the difference between groups on the global PSQI considering age and schooling as a covariable. The chi-square test was used to compare the groups in terms of the frequency of sleep qualified as "good" or "bad", as well as sex and the complaints of sleep problems before and after stroke.

The association between demographic variables (sex, age, and schooling), clinical variables (cerebral hemisphere affected, neurological degree and post-lesion time) and the PSQI components (latency, duration, efficiency and daytime dysfunction) was established, considering them all as independent variables. These variables were analyzed with the global PSQI (dependent variable) to establish the entry order of the variables. Next, explanatory models were constructed with linear regression analysis to identify the variables that predicted the subjective quality of patient sleep. Following univariate analysis, the variables with p value < 0.05 were selected and, using the regression model, added one by one in decreasing order of

the correlation coefficient and by significance (*stepwise forward*). The correlation matrix (Pearson correlation test) checked for the presence of confusion variables and of multicollinearity (correlation approaching +1 or -1), in order to avoid overlap between independent variables in the regression model.

RESULTS

The groups did not show any significant difference where the sex variable was concerned ($p = 0.139$). This was not the case when schooling ($p = 0.016$) or age ($p = 0.002$) were considered: the patient group had a higher mean age and a higher percentage of subjects with 6 years of schooling or less (72.5%). NIHSS scores varied from 4 to 19 (7.7 ± 3.5), and showed reduced muscular force and motor coordination of the upper and lower limbs as well as sensitivity deficits and muscular hypertonia. This indicated a moderate degree of neurological compromise.

In agreement with the PSQI analysis, 57.5% of patients suffered poor sleep quality, whereas only 26.7% of the healthy individuals showed the same result ($p = 0.01$). A significant difference between groups was found for mean global age and schooling adjusted PSQI values (mean ± standard deviation; patients: 6.3 ± 3.5; healthy: 3.9 ± 2.2; $p = 0.002$). Patients also confirmed an increased prevalence of post-stroke sleep problems: difficulty falling sleep (before: 30.8%; after: 69.2%), and fragmented sleep (before: 35%; after: 65%).

A significant correlation between the global PSQI and the sex variable was determined ($r = 0.33$; $p = 0.037$) but no correlation was found with age ($r = 0.19$; $p = 0.228$) and schooling ($r = -0.227$; $p = 0.159$), or with the clinical variables (affected cerebral hemisphere: $r = 0.083$; $p = 0.612$; neurological degree: $r = 0.008$; $p = 0.963$; lesion time: $r = -0.081$; $p = 0.621$). However, the PSQI components showed significant correlations when compared with sleep latency ($r = 0.667$; $p = 0.001$), duration ($r = 0.448$; $p = 0.004$) and efficiency ($r = 0.728$; $p = 0.001$) as well as daytime dysfunction ($r = 0.623$; $p = 0.001$). Owing to this, these variables and the sex variable were selected for inclusion in the multiple linear regression model, in order to evaluate the predictor value of each variable in sleep quality.

The variables were added one by one, and the behavior of the model was observed as each variable was introduced. After regression analysis, it was found that sleep efficiency, latency, duration and daytime dysfunction contributed significantly to the global PSQI value. Thus, model 4 was chosen since it best explains sleep quality variation (R^2 adjusted = 0.78) (Table 1). According to this relationship, each increase in the efficiency score represents a decrease of 2.057 in sleep quality, in addition to an increase of 1.476 for daytime dysfunction, 1.221 for sleep latency, and 0.784 for sleep duration.

DISCUSSION

This study shows that stroke patients suffer from lower sleep quality than that of healthy individuals. This is supported by a higher global age and schooling adjusted PSQI average for the patient group. Campos et al.[11] found the same results when studying sleep quality in the chronic stage of stroke recovery.

Table 1. Multiple linear regression models (*stepwise forward*), considering sleep efficiency, latency and duration, daytime dysfunction and sex as independent variables. The global Pittsburgh Sleep Quality Index (PSQI) is the dependent variable.

	R^2 adjusted	b ± ET	IC 95%	*p*
Model 1	0.52			
Sleep efficiency		4.289 ± 0.655	2.962-5.615	0.0001
Model 2	0.68			
Sleep efficiency		3.226 ± 0.585	2.041-4.411	0.0001
Sleep latency		1.387 ± 0.310	0.760-2.015	0.0001
Model 3	0.76			
Sleep efficiency		2.551 ± 0.533	1.470-3.632	0.0001
Sleep latency		1.230 ± 0.269	0.684-1.776	0.0001
Daytime dysfunction		1.414 ± 0.375	0.654-2.175	0.001
Model 4	0.78			
Sleep efficiency		2.057 ± 0.563	0.913-3.200	0.001
Sleep latency		1.221 ± 0.258	0.698-1.744	0.0001
Daytime dysfunction		1.476 ± 0.360	0.745-2.207	0.0001
Sleep duration		0.784 ± 0.378	0.016-1.551	0.046
Model 5	0.79			
Sleep efficiency		2.012 ± 0.560	0.873-3.151	0.001
Sleep latency		1.160 ± 0.261	0.630-1.690	0.000
Daytime dysfunction		1.347 ± 0.373	0.589-2.105	0.001
Sleep duration		0.901 ± 0.388	0.113-1.690	0.026
Sex		0.746 ± 0.613	-0.500-1.992	0.232

They also observed an increase in sleep duration and more daytime napping. According to the authors, these alterations seem to compensate for worsened sleep quality in patients, suggesting that they suffer behavioral changes that compensate for the effects of a stroke.

In this study, no relation was found between the global PSQI and age or schooling, even though studies have reported a correlation between alterations in sleep quality and advanced age[12] as well as a relationship between poor sleep quality and low social class[13]. This can be explained by the fact that no elderly individuals were included in the study sample and that the schooling did not vary greatly among the patients.

The clinical variables were not found to be associated with sleep quality evaluated by the PSQI. Bassetti & Aldrich[14], who studied the effects of acute hemispherical stroke on sleep, did not find significant differences between stroke patients affected in the right or left hemisphere. As in our study, they found that aspects of sleep were not affected by the hemisphere in which the lesion was located. These authors also report that acute left or right hemisphere stroke is accompanied by alterations in electroencephalographic recordings during sleep that are correlated with stroke severity. In addition to the studies using different methodologies (objective measurement versus subjective measurement), the divergence associated with lesion severity can be explained by the fact that the patients of the present study showed little difference in the amount of neurological damage. Furthermore, since most of the patients were in the chronic post-stroke stage, this might have favored the

non- association between post-lesion time and sleep quality. This shows the importance of long term studies that evaluate fluctuations in sleep quality throughout the patient's clinical evolution. The greater prevalence of patients with sleep disturbances after stroke suggests an association between this pathology and sleeping problems.

The specific way in which stroke compromises sleep quality by interfering in the sleep mechanism has not been greatly debated. Sleep regulation involves two basic processes: the homeostatic (process S) and the circadian (process C). The homeostatic process is responsible for the increased propensity toward sleep during wake times and a decrease during sleep times. The circadian process promotes the temporal organization of the sleep-wake cycle and through alert mechanisms maintains wakefulness during the day, thus facilitating sleep consolidation at night. Several brain neurotransmitter or neuromodulator systems have been strongly implicated in such processes[15].

Disruption of wake- or sleep-promoting pathways results in behavioral state instability. There is evidence that the homeostatic and circadian process may be affected separately. In this sense, compromised sleep regulation may depend on the location of the stroke. The study of patients with subcortical stroke and compromised hypothalamus suggests a functional interruption of the suprachiasmatic nucleus, which affects the promotion of wakefulness in the circadian process, causing alterations in alertness, expressed mainly by diurnal somnolence in the patients[16]. On the other hand, Beloosesky et al.[17] studied melatonin rhythms in post hemispheric stroke patients. The authors detected persistent rhythmicity of melatonin production, indicating that the circadian process and the neural connection for the pineal gland were not affected.

In the present study, multiple linear regression analysis showed that the strongest predictor of poor sleep quality was compromised sleep efficiency, which may indicate less deep or intense sleep. We can associate this result with the high prevalence of difficulty in falling asleep and fragmented sleep. Müller et al.[6] found that stroke patients woke more often after falling asleep and had less sleep efficiency than the control group. Considering that insomnia is defined as a difficulty to fall or stay asleep, or as non-restorative sleep that compromises daytime functioning, the complaints of difficulty in falling asleep and of fragmented sleep suggest the occurrence of insomnia in this study sample. This conclusion was also reached in a study by Leppävuori et al.[18], who found that insomnia was a common complaint after ischemic stroke. Daytime dysfunction, latency and sleep duration were also considered predictors of patient sleep quality. Foley et al.[7] who evaluated the association between sleep problems and chronic illnesses, concluded that stroke is associated with the presence of one or more sleeping problems.

Likely a hemispheric stroke does not reach the subcortical structures or the neural pathways of the hypothalamus related to the circadian system, but the cortical injuries mainly in the sensory motor cortical areas can result in a reduction of *inputs* involved in the *feedback* mechanism of homeostatic sleep regulation, resulting in a difficulty to fall and stay asleep, thus compromising sleep quality, expressed first by decreased sleep efficiency and second by increased daytime dysfunction, latency and sleep duration (Figure 1). The electroencephalographic data of the Vock et al.[8] showed changes in NREM sleep, sleep efficiency and alertness after sleep onset, which could also support the idea of compromised process S of sleep regulation. This interpretation is based on the fact that process S derives from a physiological variable EEG slow wave activity (SWA). When sleep episodes are shortened, SWA increases in NREM sleep, expressing a greater need for deep sleep, and decreases immediately after the first night of sleep recovery[19].

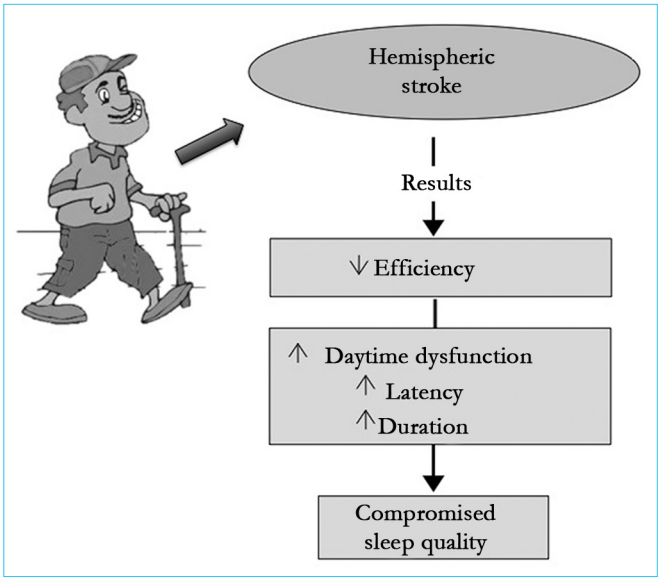

Figure 1. Schematical drawing of hemispheric stroke influence on sleep quality. Hemispheric stroke likely results first in reduced sleep efficiency and second in increased daytime dysfunction, latency and sleep duration, thus compromising sleep quality.

The aim of the hypothesis raised in the present study is to stimulate a discussion about how sleep regulating mechanisms are affected after a hemispheric stroke, leading to compromised sleep quality. We are carrying through studies with actigraphy and polysomnography to confirm this hypothesis. Moreover, the findings are not sufficient to definitively affirm that the homeostatic process is affected isolatedly in hemispheric stroke cases, because we cannot rule out the possibility of changes in the interaction with the circadian process.

This study had certain limitations. The patients did not have the different degrees of neurological compromise needed to evaluate the fluctuations in sleep quality clinically associated with this affliction. Nor did this study examine the relationship between sleeping problems and the location of specific cerebral lesions. This was because the neuroimaging examinations were carried out at different hospitals, making the standardization of the medical reports impossible. The lack of sleep apnea screening should be included as a study limitation. Furthermore, it would be important to analyze the influence of the circadian system on the sleep regulation of these patients.

CONCLUSION

This study confirmed that stroke patients have compromised subjective sleep quality mainly associated with alterations in sleep efficiency. This was compensated with increased daytime dysfunction, latency and sleep duration. From a therapeutic point of view, the results of this study point to the need for investigating stroke patient sleep patterns in more detail. We suggest that complaints of poor sleep quality be given priority assessment during clinical diagnosis. Treatment strategies of sleep medicine should be taken, since sleep alterations can compromise the cognitive and motor rehabilitation process of these patients.

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Sleep Science

ORIGINAL ARTICLE

Why modeling? Mathematical models of the human sleep/wake cycle gives new insights on the pathophysiology of fatal familial insomnia (FFI)

Porque fazer modelos? Modelos matemáticos para ciclo de vigília/sono em humanos, fornecem novos insights na fisiopatologia da insônia família fatal (IFF)

Garay Arturo[1], Susana Blanco[2]

ABSTRACT

FFI, a rare prion disease, constitutes by their wake and sleep abnormalities a unique pathophysiological model of disease. Recently, a neurobiological-mathematical model of the human sleep/wake cycle (MMSWC) developed by Rempe, BestJ and Terman, reconciles circadian/homeostatic influences with new findings like the proposed sleep/wake flip-flop switch and REM-NoREM switch. We attempt now to modeling sleep abnormalities seen in FFI patients with the hypothesis that different degrees of perturbation (activation/deactivation) of circadian and homeostatic drives are related with sleep findings previously reported. We modeling our sleep data using MMSWC, where, briefly, the ventrolateral preoptic neurons (VLPO) and monoaminergic neurons (AMIN) inhibit each other and are modeled as a system of two ordinary differential equations. A similar interaction between REM-on and REM-off was also implemented. Both models were able to produce simulations that we confront with reanalyzed polysomnograms of a proven and peculiar case of FFI. IntraREM sleep fragmentation, the cyclic alternating pattern reported in atypical REM sleep and the reversal of atypical REM-NoREM presentation, seen in our case of FFI, can be simulated according the MMSWC by increasing random and Poisson perturbations on circadian and/or REM-on inputs. This was made by modifying the term I AMIN that corresponds to REM-on equations of this model. These mathematical models support the hypothesis that in FFI the extended neuronal network that regulates sleep and wakefulness could be disrupt by altered circadian/homeostatic and REM inputs.

Keywords: fatal familial, insomnia, mathematical models, sleep disorders.

RESUMO

A IFF é uma doença priônica rara constitui por alteração no estado de vigília e do sono, um modelo fisiopatológico único de doença. Recentemente, um modelo neurobiológico-matemática do ciclo vigília/sono humano (MMSWC), desenvolvido por Rempe, Best J e Terman, concilia influências circadianas/homeostático com novas descobertas, como proposta de alternância sono/vigília flip-flop e alternância REM-Norem. Tentamos agora fazer um modelo dealterações do sono observadas em pacientes FFI com a hipótese de que diferentes graus de perturbação (ativação/desativação) de unidades circadianas e homeostáticas estão relacionadas com as conclusões do sono relatadas anteriormente. Nós modelamos nossos dados de sono usando MMSWC, onde, imediatamente, os neurônios pré-óptica ventrolateral (VLPO) e neurônios monoaminergic (AMIN) inibem um ao outro e são modelados como um sistema de duas equações diferenciais ordinárias. Também foi implementada uma interação semelhante entre REM e REM-on-off. Ambos os modelos foram capazes de produzir a simulações enfrentadas ao reanalisar a polisonografia de um caso comprovado e peculiar da IFF. A fragmentação do sono intra-REM, o cíclico do padrão alternado no sono REM atípico e a reversão de apresentação atípica REM/NREM, visto em nosso caso de IFF, pode ser simulada de acordo com o MMSWC, aumentando a perturbações aleatórias de Poisson em circadiano e/ou REM-no input. Isto foi feito através da modificação do termo que AMIN correspondente a REM na equações desse modelo. Estes modelos matemáticos apoia a hipótese de que na IFF a rede neuronal prolongada que regula o sono e o estado de vigília pode ser perturbar pelas alternancias circadianas/homeostática e REM inputs.

Descritores: insônia familiar fatal, modelos matemáticos, transtornos do sono.

INTRODUCTION

FFI, a rare prion disease characterized by the Met129, Asn178 haplotype, constitutes by their wake and sleep abnormalities a unique pathophysiological model of disease[1]. It was first described by Lugaresi et al.[2], as a disease caused by a selective degeneration of the anterior and dorsal-medial thalamic nuclei. Clinically, the affected patients presents progressive insomnia with inability to produce physiological patterns of slow wave sleep (SWS), abnormal REM sleep behavior, dysautonomia, myoclonus and progressive dementia [3-7]. We have previously demonstrated, in a proven and peculiar case of FFI, the presence of reduced sleep time, typical absence of sleep spindles, atypical NREM sleep ("aNREMsleep"), fragmented atypical REM sleep ("aREMsleep") and reversal

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"aREMsleep" - "aNREMsleep" presentation[8-10]. This case, also seems to present some inherent "ultrashort ultradian periodicity" resembling a behavior that we characterized like a cyclic alternant pattern (CAP) during "aREM sleep"[11]. Recently, a neurobiological-mathematical model of the human sleep/wake cycle developed by Rempe et al.[12] based on physiological processes and interaction between neuronal cell groups reconciles circadian/homeostatic influences with new findings like the proposed sleep/wake flip-flop and REM-NoREM sleep switch[13]. Thus, this model can be applied to tests hypothesis about our findings and we attempt now to modeling sleep abnormalities seen in this case of FFI with the hypothesis that different degrees of perturbation activation/deactivation of circadian and homeostatic drives are related with sleep findings previously reported.

MATERIAL AND METHODS

We used the Mathematical Model of Sleep/Wake Cycle of Rempe et al. (MMSWC)[12] producing simulations that we confront with reanalyzed polysomnograms of our case of FFI.

Polisomnograms (PSGs) (PSGs, n = 5) were performed on 21 channels with a Nihon-Khoden polygraph. Scalp electrodes were placed according to 10-20 system in bipolar montage. During PSGs the following variables were monitored: electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), nasal and oral airflow, thoracic and abdominal effort, and pulse oximetry. Sleep-wake patterns were scored in 30 sec. epochs using standard criteria[14]. We use 5 polisomnograms, the best that we obtained, without artifacts.

"aREMsleep" (Figure 1) was characterized by briefs bursts of EEG desynchronization, low amplitude submental EMG, rapid eye movements, and brief phasic muscle twitches, and atypical NREM sleep by periods of low amplitude theta-delta activity without spindles. Measures of sleep continuity, architecture and REM sleep parameters were performed. Hypnograms were analyzed using spectral analysis of the frequency components from Fast Fourier Transform (FFT) of the raw data. "aREMsleep" periods were defined as episodes separated by at least 30 min. of clock time. "aREMsleep" - "aREMsleep" cycles were defined as the time from the end of "aREMsleep" period to the end of the next.

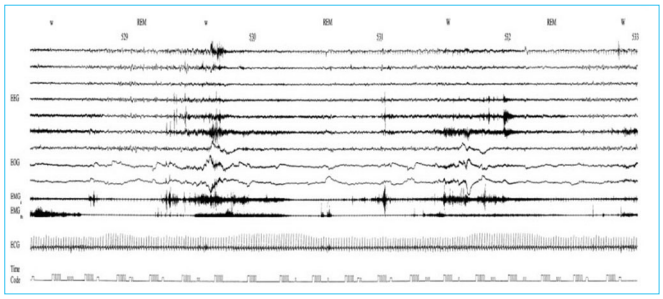

Figure 1. Polygraphic records showing the "aREMsleep" - wakefulness oscillations. EEG: electroencephalography; EOG: electrooculography; EMG: electromiography, digastric (d) and tibial (Tb); ECG: electrocardiography.

Hypnograms were also analized using spectral analysis of the frequency components from Fast Fourier Transform (FFT) of the raw data (30 seconds epochs).

All results are expressed as mean ± SEM and Student´s *t* test was used to compare differences between means. Nonparametric tests, not paired, using INSTAT-GRAPHPAD statistical software were used to determine differences and a probability less than 0.05 was considered significant.

Model of the Human Sleep/Wake Cycle of Rempe et al. (MMSWC)

This mathematical model accounts for several aspects of the human sleep/wake physiology including timing, ultradian, circadian and homeostatic dynamics based on previous "flip-flop" models[12]. A flip-flop switch could be conceptualized as a circuit containing mutually inhibitory elements, where each neuronal pool inhibits the other and disinhibits its own action and were first design by electrical engineers to produce discrete states with sharp transitions avoiding transitional states. This type of circuits are avoiding transitional states, making a wake-sleep system able to do rapid transitions and thus, behaviourly, with the capacity to respond very fast to external or internal stimuli without transitional states.

The model includes the sleep-promoting neurons in the ventrolateral preoptic region of the hypothalamus (VLPO), the wake-promoting monoaminergic cell groups (AMIN), orexin neurons (ORX), a circadian pacemaker corresponding to activity within the suprachiasmatic nucleus (SCN), and input from cortical areas (Figure 2).

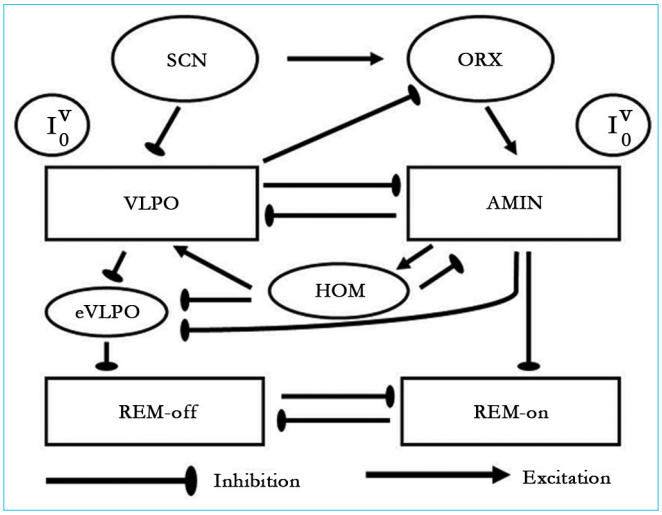

Figure 2. Block diagram of the mathematical model of the human sleep/wake (MMSWC).

The Model assumes that there is a sleep homeostat, (HOM), that increases while awake and decreases during sleep. The VLPO and AMIN are each modeled as a system of two ordinary differential equations. The authors defined eight parametric differential equations that represent Sleep/Wake and REM/NoRem cycles. We replaced the additive noise defined by

the authors and we introduced linear and non linear noise inside the circadian pacemaker as a new and effective way to obtain the best representation of the REM fragmentation in cases of FFI. These modifications do not change the dynamic and the concepts of previous model.

Rempe, Best and Terman Equations

The original Rempe, Best and Terman equations are:
For Sleep/wake cycle (Figure 3).

$$x'A = 1/dA\ (fA(xA, yA) - IVLPO + IORX + IoA - IHOM + InA)$$
$$y'A = gA\ (xA, yA)\ (7\ a,b)$$

and

$$x'V = 1/dV\ (fV(xV, yV) - IAMIN + ISCN + IoV - IHOM + InV)$$
$$y'V = gV\ (xV, yV)\ (8\ a,b)$$

where

$$f(x, y) = 3x\text{-}x3 + 2 - y$$
$$g(x, y) = e(gH(x) - y)/t(x)$$
$$IVLPO = gvlpo\ H(xV)$$
$$IAMIN = gaminH(xA)$$
$$ISCN = gscn\ C(t)$$

gvlpo, gamin and *gscn* are constants. *H* is the Heaviside function and *C(t)* represent the circadian pacemaker.

For REM/nREM cycle the corresponding equations are:

$$x'R = s'\ (fR(xR, yR) - IAMIN + INREM + IoR + InR)$$
$$y'R = s(gR\ (xR, yR))\ (9\ a,b)$$
$$x'N = s'\ (fN(xN, yN) - IeVLPO + IREM + IoN + InN)$$
$$y'N = s(gN\ (xN, yN))\ (10\ a,b)$$

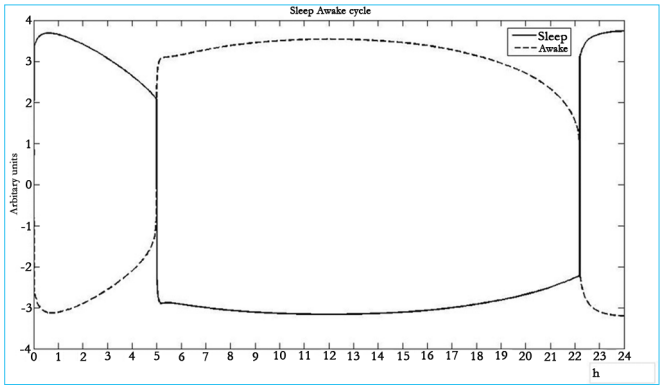

Figure 3. Modeled sleep and waking cycles.

RESULTS

Clinical Data

Briefly, reduced Total Sleep Time, "aNREM sleep" without spindles, fragmented and reduced "aREMsleep" time, sleep onset "aREMsleep" periods, reversal of aNREMsleep-aREM sleep presentation and a ultrashort ultradian "aREMsleep" rhythmicity characterized our case of FFI (Figures 4-6 and Table 1).

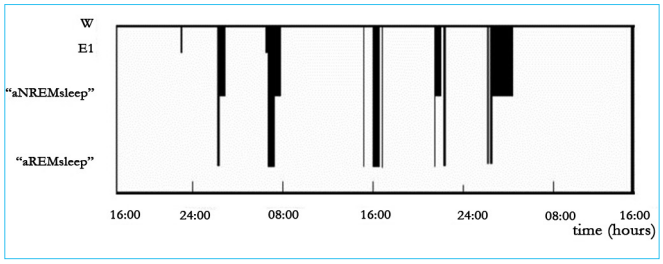

Figure 4. Hypnogram representing the occurrence of sleep during an extended PSG (48hs-dimlight conditions).

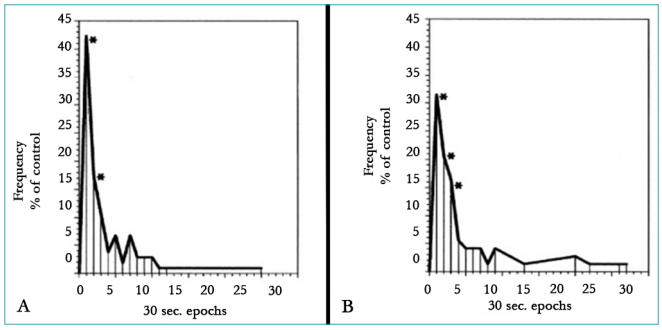

Figure 5. Periodographs showing "intra aREMsleep" (a) and "intra aREMsleep" wakefulness episodes (3b) ranging 30 to 90 seconds. * $p < 0.05$; Kruskall-Wallis NP Test; Dunn's NC Test.

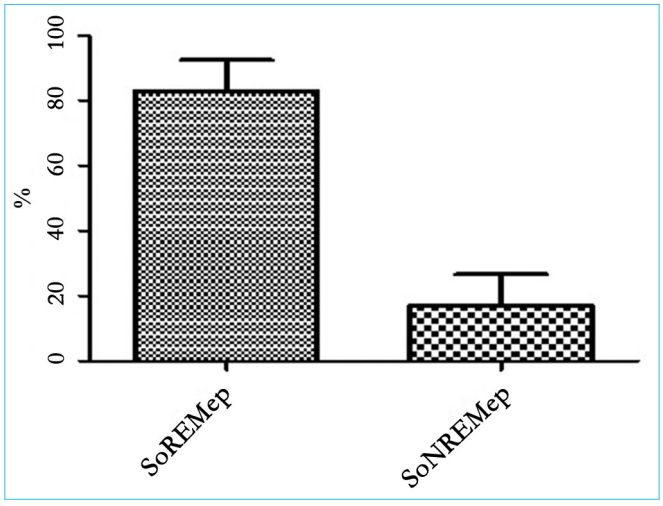

Figure 6. Frequency of sleep-onset "aREMsleep" and "aNREMsleep" episodes.

Simulations

Fragmentation effect on REM sleep introducing a noisy circadian pacemarker

The dynamics of the REM On-Off cycle were modified with noise. A noisy circadian pacemaker $C(t) = A\ (\sin\ (Q\ w\ t) + \cos\ (Q\ w\ t)) + Em(t)$ is applied (Figure 7). *Q* represents random noise, and *Em(t)* is again modeled by Macro Poisson shot noise process *N(t)*, having random pulse amplitudes and duration, which is channelled through simple exponential decay dynamics given by eq.(5).

Table 1. Polisomnograms data.

TST (%TRT)	8.3 ± 3.8
W (% TRT)	89.1 ± 3.4
Stg. 1 (% TRT)	3.2 ± 2.8
"aREMsleep"(% TRT)	5.3 ± 2.4
"aREMsleep" aw/h (#)	43.5 ± 10.3
"aREMsleep" eff (%)	37.3 ± 10.5
"aNREMsleep"(% TRT)	2.4 ± 1.6
"aNREMsleep" aw/h(#)	2.8 ± 2.8
"aNREMsleep"eff (%)	94.1 ± 7.2
"aREMsleep" P1 (min)	6.0 ± 2.8
"aREMsleep" P2 (min)	1.0 ± 0.7
"aREMsleep" P3 (min)	18.4 ± 10.1
"aREMsleep" C1(min)	98.1 ± 30.4
"aREMsleep" C2 (min)	96.1 ± 31.6

$p < 0.05$; "aREMsleep" p1-2 vs. "aREMsleep" p3.

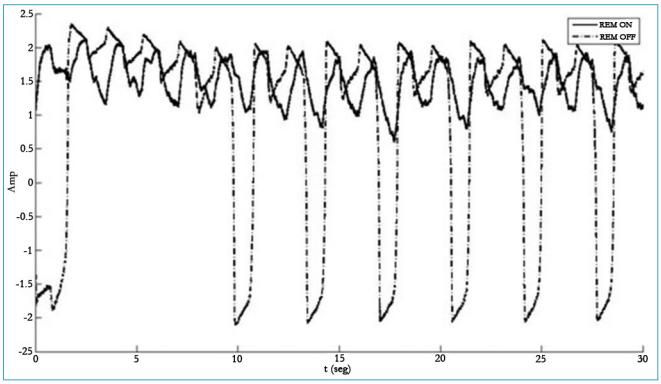

Figure 7. MMSWC simulation: REM On-Off cycle with noise.

The Macro poissonian process has the following characteristics: pulse inter arrival times exponentially distributed with mean l = 1.1, pulse amplitude uniformly distributed on {1.25, 25} and pulse durations uniformly distributed. Note that *Em* is a linear term and Q is a non-linear one. The increase in the amplitude of the noisy terms produced a scale change in the flip-flop model, fragmentating the REM/NREM and Sleep/Wake cycles.

Reversal of NREM-REM sleep presentation

Reducing iVLPO and including a noise term in each of the models of the four main cell groups does not qualitatively alter the sleep-wake behavior. However, introducing noise is an important element in making the model correctly reproduces the SoREMP data and the reversal of "aREMsleep-aNREMsleep" presentation (Figure 8). Without noise the model does not exhibit SoREMP at any circadian phase.

CONCLUSION

The oscillations observed in this case of FFI, can be compared with the oscillations obtained using the MMSWC model. In the framework of MMSWC a noisy circadian pacemarker produced

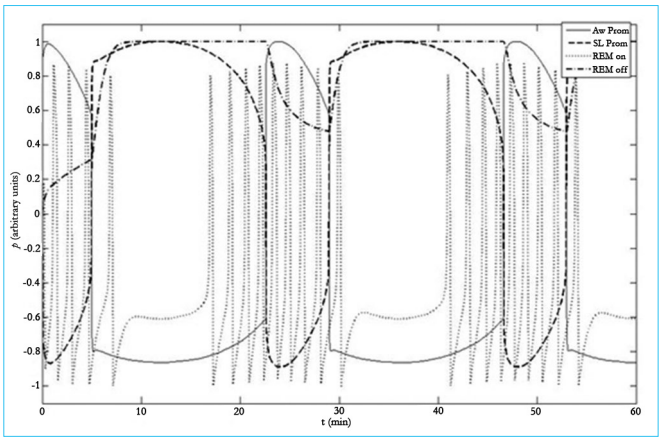

Figure 8. MMSWC simulation: Reducing iVLPO and including a noise term in each of the models of the four main cell groups.

REM sleep fragmentation. Thus, near one-minute centered cyclic alternating pattern in intra"aREMsleep" periods could be explained by circadian alterations into the dynamics of the model. This type of short-ultradian arousability, described by Terzano et al.[15,16] and also observed in this case of FFI during "aREMsleep" meaning a rol of thalamolimbic system in regulation of sleep and homeostatic-circadian functions during REM sleep. Also, the CAP sequences simulated by MMSWC and the presence of preserved ultradian rhythmicity of "aREMsleep" periods observed in our case of FFI, suggest that the oscillator regulating episodic "aREMsleep" periods continues to function during shorts periods of wakefulness[17].

The MMSWC model simulates the reversal of REM-NREM sleep presentation observed in our case of FFI. As we shown MMSWC leads to several insights and predictions concerning the human sleep/wake cycle. For example, the model predicts that during the normal sleep/wake cycle, both waking up, falling asleep and also REM dynamics are driven by the activity of VLPO. A specific role of the hypothalamus in regulating REM sleep is also suggested by the appearance of so-called sleep-onset REM periods in patients with narcolepsy and with hypothalamic lesions[18]. Thus, MMSWC support the hypothesis that in FFI the extended neuronal network that regulates sleep and wakefulness could be disrupt by thalamo-limbic disfunction disturbing circadian/homeostatic and REM inputs[19].

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Sleep Science

ORIGINAL ARTICLE

The effect of eye mask on sleep quality in patients of coronary care unit

O efeito da mascara de olhos na qualidade de sono em pacientes em uma unidade coronariana

Fateme Mashayekhi[1], Mansour Arab[2], Motahhareh Pilevarzadeh[1], Masoud Amiri[3], Hossein Rafiei[4]

ABSTRACT

Objectives: Patients in coronary care unit (CCU) are at risk of sleep deprivation. This study investigated effects of eye mask on sleep quality in patients of CCU in Southeast of Iran by a cross-over design. **Methods:** Using Verran and Snyder-Halpern Sleep Scale (VSH Sleep Scale), quality sleep of 60 patients with and without usage of eye mask were evaluated. This tool consists of 16 items that includes three main sleep sub scales: disturbance, effectiveness, and supplementation. **Results:** In total, 34, 22 and 4 out of 60 patients were admitted to CCU due to myocardial infarction (MI), chest pain and angina pectoris, respectively. Mean time of patients' nocturnal sleep was 6.6 ± 1.1 hours. Using eye mask have statistically significant increased the quality of sleep in subscales disturbance and effectiveness ($p < 0.05$). **Conclusion:** In general, the use of eye mask is an easy and cheap method to improve the quality of sleep in CCU patients.

Keywords: heart diseases, sleep, sleep deprivation.

RESUMO

Objetivos: Pacientes em Unidade Coronariana (UCO) apresentam maior risco de privação do sono. Este estudo investigou os efeitos do uso da máscara de olho na qualidade do sono em pacientes do UCO no sudeste do Irã, com um desenho de estudo transversal. **Métodos:** Usando Verran e Snyder-Halpern Scale Sleep (VSH Escala do sono), sono de 60 pacientes com e sem o uso de máscara de olho a qualidade foram avaliada. Esta ferramenta é composta por 16 itens, que inclui três principais sub-escalas do sono: perturbação, eficácia e suplementação. **Resultados:** No total, 34, 22 e 4 de 60 pacientes foram internados em UCO devido ao infarto do miocárdio (MI), dor no peito e angina respectivamente. O tempo médio de sono noturno dos pacientes foi de 6,6 ± 1,1 horas. Os pacientes que usaram máscara de olho apresentaram estatisticamente significativa aumentou a qualidade do sono nas sub-escalas de perturbação e eficácia ($p < 0,05$). **Conclusão:** Em geral, a utilização de máscara para os olhos é um método fácil e barato, para melhorar a qualidade do sono em pacientes UCO.

Descritores: cardiopatias, privação do sono, sono.

INTRODUCTION

Sleep composes one third of human life and is an essential part of the normal human circadian rhythm[1,2]. Good sleep could reduce stress and anxiety which it may help the person by a restorative process, increase focus attention, consistency and enjoyment of daily activities[3]. Although the function of sleep is not clear, it is generally accepted that lack of sleep could affect on the health of patients and may tend to a recovery from illness[4-7]. In general, hospitalization can affect patients' quality of sleep[7,8]. It can be related to environmental, physiological and psychological factors[6,9]. Acutely, ill patients are at higher risk of sleep disruption[3,10,11], especially critically ill patients in coronary care unit (CCU)[3,12]. Many forms of sleep deficit can occur in patients who admitted to CCU; including decrease duration of sleep, difficulty in falling asleep, and difficulty maintaining sleep during the night[3].

In critical care setting, two main causes of sleep deprivation are noise and inappropriate use of light/dark cycles[10]. Although most sleep disorders in CCU patients could be treated by using pharmacological methods[3,12,13]; however, non-pharmacological methods still remain important and less expensive way for increasing quality of sleep in hospitalized CCU patients[3,12]. The effectiveness rate of these therapeutic methods has been reported 70 to 80%[13]. Moeini et al.[12], in 2012, studied the effects of aromatherapy on the quality of sleep in CCU patients. They reported that quality of nocturnal sleep in patients with ischemic heart disease could improve after aromatherapy with lavender oil. In the study of Hu et al.[14], the effects of earplugs and eye masks on nocturnal sleep, level of urine melatonin and cortisol in healthy subjects exposed to simulated intensive care unit environment were evaluated. They reported that the use of earplugs and eye masks may increase

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rapid eye movement (REM) time, decrease REM latency, less arousal and elevate level of melatonin in urine. They also reported that for patients, the use of eye mask is more comfortable than earplug[14]. In 2010, Neyse et al.[3] surveyed the effect of earplug on the quality of sleep in sixty patients with acute coronary syndrome whom were admitted in CCU. They reported that the use of earplug resulted improvement in the quality of sleep in this group of patients. They also reported that use of earplug by CCU patients has decreased consumption of sleeping medications and increased the morning function.

Furthermore, sleep deficit may increase activity of sympathetic system which in turn could result in increased heart rate, blood pressure, myocardial oxygen demand, pain, anxiety, irritability and nervousness in patients with heart diseases[3,12]. Health care team members should pay more attention to patients' sleep in CCU. In this regard, the use of non-pharmacologic interventions such as eye mask is a cheap and easy method[3]. Despite the emphasis on the use of non-pharmacologic methods for improving patients' sleep quality in CCU, few studies have been performed in this area. The purpose of this study was to evaluate the effects of eye mask on sleep quality in CCU patients in Southeast of Iran.

MATERIAL AND METHODS

The study was conducted during the period of July to October 2012 in Jiroft Hospital in Southeast of Iran. Ethical approval was obtained from the research ethical centre of the Kerman Medical University. A cross-over design was performed. The sample composed of 60 patients who were admitted in CCU. This unit has 8 beds in 8 separated rooms. According to hospital protocol, at 22:30 every night, all lights were turned off for helping patients to have a better sleep. A "night's sleep" is considered as the period from when the person tried to sleep until waking up in the morning[15].

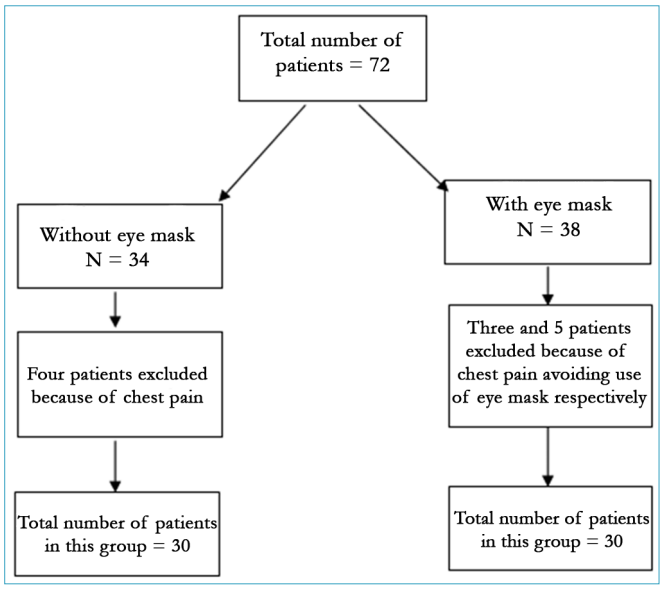
Written consent was obtained from each participant. Before obtaining the patients' consent, the research was comprehensively described to each patient, and they were assured that their information will be used only for research purposes. Inclusion criteria of the study were: aged more than 18 years old, being alert enough to response the questionnaire, have stable hemodynamic situation, no history of vision's disorders, and not used previous eye mask at sleep time. Patients with previous sleep disorder (acute or chronic), patients with history of mental disorder and patients who used narcotics, sedative, psychiatric and analgesic drugs were excluded. In time of CCU admission the eligible patients were randomly assigned to two groups (group eye mask (group 1) or without eye mask (group 2) by the supervisor of the CCU, who chose the next serially numbered sealed opaque envelope containing a simple 1:1 randomization sequence. Patients in group1 used eye mask in sleeping time in first night after admission to CCU and patients in group 2 slept without eye mask at first night after. In second night patients groups changed. Sampling continued to sample number reached to 60 patients. Patients' room and beds were similar in both nights for every patient. Correct use of eye mask by patients was controlled by researchers working in CCU.

Data collection tools in this study were Verran and Snyder-Halpern Sleep Scale (VSH Sleep Scale). Using this questionnaire, patients provided an assessment of the quality of their previous night's sleep. This tool consists of 16 items which includes three main sleep sub scales: "disturbance" (interruptions and delays in sleep), "effectiveness" (how well sleep-refreshed the individual), and "supplementation" (napping). Disturbance comprises items measuring subscales of fragmentation (interruption of sleep) and "latency" (delay in getting to sleep). Effectiveness comprises the subscales of "quality" (restfulness and depth of sleep), and "length" (hours of sleep while in bed). Supplementation contains four items about naps and falling back asleep after morning awakenings. Each characteristic is measured using a 100 mm visual analogue scale and the total score for the primary outcome of sleep disturbance is a sum of the scores from each scale (total score maximum 700). A lower total score on this scale indicates a lower degree of sleep disturbance. For effectiveness, higher scores indicate better sleep[15-18]. In order to translate the English version of VAS into Farsi, the standard forward-backward procedure was applied. Translation of the items and the response categories was independently performed by six professional translators and then temporary versions were provided. Later, they were back translated into English and after a careful cultural adaptation, the final versions were provided. The validity of questioner has been assessed through a content validity discussion. Scholars of statistics, physicians and nurses have reviewed the content of the questioner. To reassess the reliability of translated questioner alpha coefficients of internal consistency. The alpha coefficient for questionnaire was 0.91. Data were analyzed with use of descriptive statistics (mean and standard deviation (SD), Chi squared test and paired *t*-test. All statistical analyses were performed using SPSS software (v15.0; PASW Statistics). A p value of less than 0.05 was considered as statistically significant.

RESULTS

Of 72 patients who surveyed to achieving sample size of 60, 7 and 5 patient were excluded because of needs to morphine for relieving pain and avoiding use of eye mask respectively (Flow Chart 1). Of the 60 patients, 34 were men. The mean age of patients was 58 ± 11.8 years. Of the 60 patient, 34, 22 and 4 were admitted to CCU due to myocardial infarction (MI), chest pain and angina pectoris, respectively. In first time, mean time of nocturnal sleep, in patients in group 1 (group eye mask) and patients in group 2 (without eye mask) were 6.3 ± 1.1 and 5.4 ± 1.9 hour respectively. In second night, mean time of nocturnal sleep, in patients in group 1 (group eye mask) and patients in group 2 (without eye mask) were 6.4 ± 1.5 and 5.2 ± 1.8 hour respectively. Mean score of sub scale "disturbance" before and after intervention was 140.90 ± 55.6 and 89.83 ± 52.1 respectively. In this sub scale, most change before and after use of eye mask was related to item "wake after sleep onset". In sub scale "effectiveness", mean score of sleep quality was 255.33 ± 41.1 before intervention and 291.50 ± 38.9 after

intervention. In this sub scale, most change before and after use of eye mask was related to item "sleep sufficiency evaluation". Results of paired *t*-test showed significant difference in mean score of sub scales "effectiveness" and "disturbance" before and after use of eye mask ($p < 0.05$). Mean score of sub scale "supplementation" before and after intervention was 25.50 ± 27 and 40.80 ± 23.4 respectively. In this sub scale, most change before and after use of eye mask was related to item "wake after final arousal (early morning awake)".



Flow chart 1: Patient's assignment to groups.

Results of paired *t*-test did not show any significant difference in sub scale of "supplementation" before and after use of eye mask ($p > 0.05$). Mean scores of three sub scale have been shown in details in Table 1.

DISCUSSION

The study was conducted in order to evaluate the effects of eye mask on the quality of sleep in CCU patients. Our results showed that in general, quality of sleep significantly improved after use of eye mask in this group of patients. In fact, hospitalized patients might experience a reduction in the amount and quality of sleep[3]. Admission to hospital may severely disrupt sleep, which can worsen pain, cardio-respiratory status, and the psychiatric health of acutely ill patients[3,12,13,19].

Quality of sleep in hospitalized patients should be a routine part of patients' assessment such as vital sign, because the patients sleep quality may reveal more information about patients' overall well-being[19]. One important group of patients whom may have higher risk of sleep disturbance is the patients with heart diseases[20]. Erikson et al.[21] studied the symptoms of sleep disturbances in patients with heart failure. They reported that 56% patients have trouble sleeping and one-third of them had used help sleeping medications. They also reported that inability to sleep flat (51%), restless sleep (44%), trouble falling asleep (40%), and awakening early (39%) are the most common problems in patients with heart failure. Similar to Erikson et al.[21], results of Zeighami et al.[22], in 2013, showed that patients whom suffer from heart disease, may have many problems in sleeping. Two most common sleep problems reported by Zeighami et al. were insomnia and sleep apnea. They also reported that factors such as weight loss, smoking cessation, control and treatment of chronic diseases and control of drugs side effects could decrease sleep problems in this group of patients.

High level of light and sound may considerably affect the quality of patients' sleep[23]. Zolfaghari et al.[24], in 2013, investigated the effects of environmental modification on quality of sleep among CCU patients. They reported that interventions of decreasing excessive environmental light and noise; such as

Table 1. Mean score of three sub scale of VSH before and after intervention.

Sub scale	Items	Mean score before intervention	Mean score after intervention	*p* value
Disturbance	Mid-sleep awakening	19.67 ± 7.30	13 ± 7.14	0.006
	Wake after sleep onset	25.17 ± 9.84	14.33 ± 10.56	0.001
	Movement during sleep	19.83 ± 10.46	13 ± 7.14	0.005
	Soundness of sleep	63.17 ± 15.79	41.33 ± 16.23	0.527
	Quality of disturbance	24.83 ± 13.48	16.83 ± 12.35	0.679
Effectiveness	Sleep latency	20.33 ± 8.89	14.33 ± 10.40	0.062
	Quality of latency	22 ± 10.87	14.50 ± 7.35	0.001
	Rest upon awakening	53.17 ± 12.35	66 ± 12.41	0.001
	Subjective quality of sleep	55.17 ± 11.48	65.67 ± 14.95	0.001
	Sleep sufficiency evaluation	31.07 ± 18.32	18.33 ± 14.34	0.001
	Total sleep time	51.17 ± 13.87	64.33 ± 9.97	0.002
	Total sleep period	38.17 ± 11.86	39.33 ± 10.36	0.001
Supplementation	Daytime sleep	7.83 ± 9.34	8.83 ± 11.11	0.625
	Morning sleep	5.17 ± 5.18	4.57 ± 5.99	0.682
	Afternoon sleep	12.50 ± 7.85	11.50 ± 7.32	0.625
	Wake after final arousal	64.33 ± 21.24	27 ± 18.69	0.005

turning off of extra lights, use of bulbs with low light, decreasing the alarm sounds level throughout the night, decreasing level of telephone ringtone during night and educating staff regarding the control of environmental excessive light and noise have improved the patient's nocturnal sleep in CCU. In 2007, Richardson et al.[10] surveyed the effects of earplug and eye mask on patients sleep in critical care unit with use of patient-rating scales. Similar to our finding, Richardson et al. reported that the use of earplug and eye mask could improve patients' sleep in critical care unit. Hu et al.[14] in 2010 studied the effects of earplug and eye mask on sleep of healthy subjects exposed to simulated intensive care unit (ICU) noise and light with use of polysomnography (PSG). Hu et al.[14] reported that exposing to simulated ICU environment causes decreasing in sleep quality, increasing light sleep, increasing REM latency, and decreasing REM sleep. They also reported that use of earplugs and eye masks may increase REM sleep and decrease REM latency and fewer arousals. In agreement with our finding, Moeini et al.[12] reported that use of non-pharmacological methods could improve patients sleep quality in CCU. They reported that the use of aromatherapy with lavender oil increase quality of sleep in patients who admitted to CCU. Jones & Dawson[25], in 2012, surveyed the effects of eye mask and earplug on CCU patients. Similar to our finding, Jones & Dawson reported that the use of simple interventions such as eye masks and earplugs could improve the sleep quality in critical care area. In Jones & Dawson study, participants reported that eye masks (28%) improved their sleep in CCU.

Healing cannot occur without nighttime lighting and a good night's sleep[26] sleep deficit and sleep without a refreshing and restorative function may increase the risk of recurrent events in patients with heart diseases[27]. Members of health care team especially nurses should pay more attention to satisfy the need of rest and sleep for CCU patients[3]. Nurses should assess patient sleep patterns routinely during hospitalization and then evaluate the need for sleep promotion strategies[28]. Results of present study confirmed that quality of nocturnal sleep in CCU patients was significantly improved after using of eye mask. Therefore, using eye mask at night time is a cheap and comfortable method, which could be recommended, for improving the quality of sleep in CCU patients.

Limitation

For measuring patients sleep time we used patients self reports. This limitation should be considered in the time of results use and interpretation.

CONFLICT OF INTEREST

Nothing to declare.

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Sleep Science

REVIEW ARTICLE

What we know about gastroesophageal reflux disease and obstructive sleep apnea?

O que sabemos sobre a doença do refluxo gastro-esofágico e apneia obstrutiva do sono?

Cristina Salles[1], Regina Terse Trindade Ramos[2], Adelmir de Souza Machado[3], Andrea Barral[4], Larissa Monteiro[5], Álvaro Augusto Cruz[3]

ABSTRACT

Objectives: The primary objective of this systematic review is assessing whether treatment of gastroesophageal disease (GERD) may reduce the apnea and hypopnea index (HAI) and the secondary objective of assessing whether there is a correlation between the HAI and gastroesophageal acid reflux. **Methods:** Using a systematic review of clinical studies that investigated the relationship between obstructive sleep apnea and GERD. The search included all cited publications up to April 22, 2012, using the keywords "sleep apnea, obstructive" AND "gastroesophageal reflux/diagnosis" OR "gastroesophageal reflux/drug therapy" OR "gastroesophageal reflux/therapy" AND "randomized controlled trial". The following electronic databases were used: PubMed, EMBASE, LILACS, MedLine, SCISEARCH, WEB of Science, CINAHL, BIREMI, SCOPUS, and the database of controlled clinical trials of the COCHANE collaboration. The total sample size was 60 patients (55% males). All patients in the eligible studies were submitted to both polysomnography and esophageal pH measurements before and after treatment. **Results:** Initially, 24 articles were selected. Of these, only three met the criteria for this study All the 3 studies found in this analysis were "before and after" clinical trials. Through the grouping of patients in our systematic review, we found a statistically significant decline in the average time of GERD after treatment, and a trend for reduction in the rate of HAI. Conclusion: The studies examined demonstrate that medical treatment of GERD may reduce apnea and hypopnea. Nevertheless, more controlled clinical trials are needed to confirm the benefits of drug therapy for GERD in the context of obstructive sleep apnea.

Keywords: adults, apnea, clinical trial, upper airway.

RESUMO

Objetivos: O principal objetivo desta revisão sistemática é avaliar se o tratamento da doenças gastro-esofágico (DRGE) pode reduzir o índice de apnéia e hipopnéia (IAH) e o objetivo secundário avaliar se existe uma correlação com o refluxo ácido gastroesofágico. **Métodos:** Utilizando uma revisão sistemática de estudos clínicos que investigaram a relação entre apnéia obstrutiva do sono e DRGE. A pesquisa incluiu todas as publicações citadas até 22 abril de 2012, utilizando as palavras-chave "apnéia obstrutiva do sono," AND "do refluxo gastroesofágico/diagnóstico" OR "refluxo/quimioterapia gastroesofágico" OR "refluxo gastroesofágico/terapia" AND "ensaio controlado randomizado". Foram utilizadas as seguintes bases de dados eletrônicas: PubMed, EMBASE, LILACS, MedLine, SCISEARCH, WEBofScience, CINAHL, BIREMI, SCOPUS, e o banco de dados de ensaios clínicos controlados da colaboração COCHANE. O tamanho total da amostra foi de 60 pacientes (55% do sexo masculino). Todos os pacientes nos estudos elegíveis foram submetidos tanto a polissonografia e a pHmetria esofágica antes e após o tratamento. **Resultados:** Inicialmente, 24 artigos foram selecionados. Destes, apenas três preencheram os critérios para este estudo todos os três estudos encontrados nesta análise foram "antes e depois" de ensaios clínicos. Através do agrupamento de pacientes em nossa revisão sistemática, encontramos uma redução estatisticamente significativa no tempo médio de DRGE após o tratamento, e uma tendência para a redução da taxa de IAH. **Conclusão:** Os estudos analisados demonstram que o tratamento médico da DRGE pode reduzir a apnéia e hipopnéia. No entanto, mais ensaios clínicos controlados são necessários para confirmar os benefícios da terapia medicamentosa para a DRGE, no contexto da apnéia obstrutiva do sono.

Descritores: adultos, apnéia, apnéia obstrutiva do sono, ensaio clínico.

INTRODUCTION

Obstructive sleep apnea (OSA) syndrome affects 4% of men and 2% of women in the United States of America[1], according to Young et al., 1993. OSA is associated with an increased risk of developing cardiovascular diseases, such as systemic and pulmonary hypertension, cardiac arrhythmias, ischemic heart disease and congestive heart failure[2]. Due to these co-morbidities, OSA is often associated with increased medical expenses, although costs can be reduced with appropriate treatments. Kapur et al.[3] showed that the mean medical cost

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per case in the year prior to a diagnosis of sleep-disordered breathing was $ 2,720, which is roughly double the cost for patients who were diagnosed and received treatment ($ 1,387).

OSA results in intermittent episodes of hypoxemia, hypercapnia, arousals, and sleep fragmentation[1] and can sometimes be caused by gastroesophageal reflux (GER). GER is considered pathological when it generates dysfunction or injury to the respiratory and/or digestive tract, at which stage it is labelled gastroesophageal reflux disease (GERD)[4].

OSA and GERD are considered separate diseases, although they share similar signs and symptoms that can overlap and become indistinguishable from each other. The incidence of GERD symptoms in patients with OSA ranges from 62% to 74%[5,6]. OSA and GERD have common risk factors including age, and obesity, and share similar aspects of pathogenesis[7].

The literature has addressed several important issues related to OSA and GERD, but many questions remain unanswered, including whether GER has a causal relationship with OSA[8]. This information has relevant therapeutic and economic consequences.

The increased prevalence of nocturnal reflux in patients with snoring and obstructive sleep apnea has been well described[9-11]. Muscle tone, including the lower esophageal sphincter and pylorus, is physiologically decreased during sleep. Due to a reduction in salivary flow and decreased motility, clearance of the esophagus is appreciably reduced relative to an awakened state[11-15]. These physiologic aspects appear to play a specific role in GERD, particularly in overcoming the upper esophageal sphincter, which is a considerably more effective reflux barrier than the lower esophageal sphincter[12,14]. The horizontal posture assumed during sleep results in higher intra-abdominal pressure with a cranially directed effect, particularly in obese individuals[9-11,13]. The pathophysiological mechanisms that have been proposed to link GERD and OSA are not mutually exclusive, and itispossible that the two conditions may interact and create a self-perpetuating positivefeedback loop[16]. This hypothesis is supported by evidence showing that treatment of GERD improves OSA and vice versa[16].

Although it has been firmly established that GERD and OSA can co-occur, the nature of the relationshipbetween the two conditions is not yet fully understood[16]. Limited data have suggested a relationship between symptomatic OSA and GERD. The prevalence of GERD has been shown to be approximately 58-62% in patients with OSA[17-19]. Apnea may increase the trans-diaphragmatic pressure and decrease the intra-thoracic pressure, favouring the development of GERD[19,20].

This systematic literature review gathered scientific evidence on the possible impact of the clinical treatment of GERD on obstructive sleep apnea. The primary objective of the review was to assess whether treating GERD reduces the incidence of apnea and hypopnea. The secondary objective was to determine if there is a correlation between the incidence of apnea and hypopnea and gastroesophageal acid reflux.

MATERIAL AND METHODS

Literature search

A systematic review of clinical studies that investigated the relationship between obstructive sleep apnea and GERD was conducted. The search included all cited publications up through April 22, 2012, using the keywords "sleep apnea, obstructive" AND ("gastroesophageal reflux/diagnosis" OR "gastroesophageal reflux/drug therapy" OR "gastroesophageal reflux/therapy" AND "randomised controlled trial." One clinical trial entitled *Proton Pump Inhibitor Therapy for Mild to Moderate Obstructive Sleep Apnea*[21] was found on clinicaltrials.gov. However, this article was excluded because the authors did not conduct polysomnographic studies nor esophageal pH measurements.

Study selection

Three reviewers independently selected articles by examining the titles and abstracts of all of the clinical studies identified in the electronic search. These evaluations were not blinded with respect to authors or the results of the studies. The following electronic databases were used: PubMed, EMBASE, LILACS, MedLine, SCISEARCH, Web of Science, CINAHL, BIREMI, SCOPUS, and the database of controlled clinical trials in the COCHRANE collaboration. Additional electronic and manual searches were conducted for cited works from the articles included in this study, using websites and national and international journals related to the topic. Inclusion and exclusion criteria, shown in Table 1, were used to screen for acceptance into the database for this study. None of the study populations were investigated more than once. A subset of the studies that met the criteria for inclusion was obtained, re-evaluated and analysed by the reviewers. The extracted data were crosschecked for consistency. All of the studies in this analysis were "before and after" clinical trials.

Table 1. Criteria for inclusion or exclusion of selected articles.

Inclusion criteria (General)
1. Articles should be in Portuguese, English, or Spanish.
2. Articles should be complete (no abstract or letter to the editor was accepted).
3. The involved individuals were over the age of 18 years.
4. Both sexes were included.
5. Any ethnicity was studied.
6. In the event that the same study resulted in multiple publications, the most comprehensive study would be accepted as the primary reference, so that no data duplication would occur.
7. Studies must involve obstructive sleep apnea; central apnea was not included.
Inclusion criteria for objectives
1. Both polysomnography and the total time of acid reflux before and after drug treatment for GER, except for treatment with cisapride and metoclopramide.
2. Apnea-hypopnea index (AHI) values, defined by the authors of the clinical trials as the number of respiratory pauses per hour of sleep, before and after drug treatment.

Continued Table 1.

3. Information related to the total time of acid reflux, defined by the authors of the clinical trials as the total time for which the esophageal pH was below 4.0, before and after drug treatment.
Exclusion criteria for the objectives
1. Diagnosis of Barrett's esophagus
2. Having undergone abdominal surgery
3. Important respiratory disorder
4. Psychiatric or neurological disease
5. Renal disease
6. Chronic liver disease

Statistical analysis

All of the identified studies were assessed for inclusion in the systematic review. Effect measures are presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs) and a significance level of $p < 0.05$. A random-effects model was used to calculate a pooled effect estimate, and the heterogeneity of the effect sizes was evaluated using the I^2 statistic. A p value < 0.05 and/or an I^2 of at least 50% was considered an indicator of substantial heterogeneity in the outcomes.

All analyses and calculations were performed using Comprehensive Meta-Analysis, version 2.2.

RESULTS

Data extraction

A total of 24 articleswere initially selected. Of these, only three met theinclusioncriteria defined for this study, as shown in Figure 1.

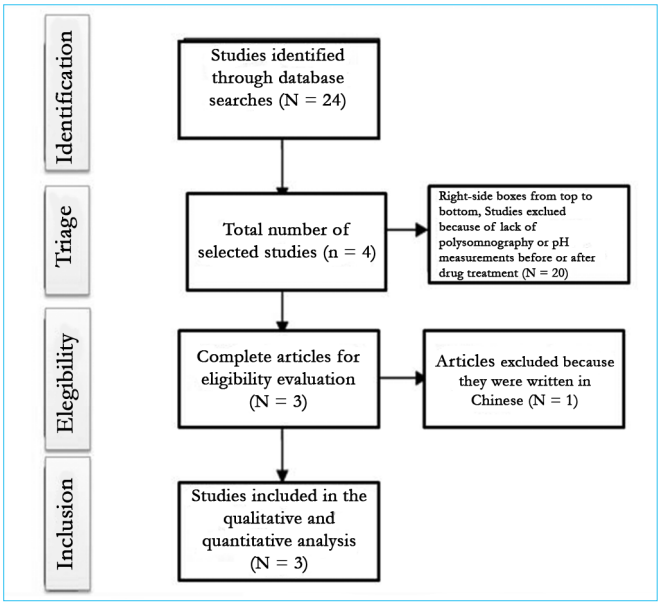

Figure 1. The process of article selection from the database.

The design characteristics of the study and outcomes are shown in Table 2. The following were major reasons for exclusion the studies did notshow any objective improvement in the sleep parameters before and after acid suppression:the authors did not adequately describe the values of the apnea-hypopnea index (AHI), which is defined as the number of respiratory pauses per hour of sleep, before and after drug treatment; the total duration of acid reflux, defined as the length of time that the esophageal pH is below 4.0, before and after drug treatment was not provided. Other studies were excluded for specific reasons. For example, Noronha et al.[23], selected infants that ranged from 1 to 6 months old; Sabaté et al.[26], selected morbidly obese patients (body mass index > 40 or > 35 kg/m^2) in association with comorbidities who were candidates for bariatric surgery; the polysomnographies performed in Watson et al.[27], 2008, were single-night diagnostic studies, and all the subjects underwent diagnostic polysomnography and were treated with CPAP within 30 days of their initial clinic visit; Dickman et al.[29], invited subjects to undergo ambulatory 24-hour esophageal pH monitoring to determine the extent of distal esophageal acid exposure, the number of acid reflux events, the number of reflux events longer than 5 minutes, and indexed their symptoms. Fifteen of the participants were randomly selected to undergo polysomnography during esophageal pH monitoring, only after treatment; Hawylkiewicz et al.[31] studied 21 consecutive patients with severe OSAS (mean AHI 44.9+/-23.8) before CPAP treatment, but none of them had any clinical symptoms of GERD; Ozturk et al.[39], 2004, investigated the respiratory and sleep parameters in patients with OSA with or without nocturnal GER episodes. Nineteen of the patients who were referred to the sleep laboratory for suspected sleep apnea were included in the study. All of the subjects underwent polysomnographic evaluation simultaneously with distal and proximal esophageal pH monitoring, but polysomnography and acid reflux before and after drug treatment for GER were not evaluated.

In Orr et al.[4] (2009), 139 participants consented to participate; but, 90 did not meet the screening criteria, and 24 dropped out of the study. As a result, only 25 patients completed both the sleep and esophageal evaluations. All participants had symptoms consistent with a diagnosis of OSA (snoring and daytime sleepiness or fatigue) and subjective complaints of GER[4]. Participants were excluded if they had a history of Barrett esophagus, history of abdominal surgery, significant respiratory distress, neurologic or psychiatric disorder, or significant chronic renal or liver disease[4]. Patients were subjected to powerful acid suppression (rabeprazole 20 mg, twice a day) for 2 months. Patients were assessed with full polysomnography and 24-hour esophageal pH monitoring, before and after treatment with powerful acid suppression.

Friedman et al.[22] (2007) which reported the phase 2 results of a two-part study designed as a prospective clinical trial, studied 52 patients with GERD and OSA. During follow-up, 14 of the patients dropped out and 9 were excluded because GERD did not improve after drug treatment. These cases were considered treatment failures and were analysed accordingly. Patients with comorbid conditions of GERD and OSA proven by 24-hour pH-monitoring studies and overnight

Table 2. Selection of articles that were identified through electronic searches.

Study ID	Polysomnography before and after treatment	pH evaluations before and after treatment	Treatment with proton pump inhibitor (for at least 4 weeks)	Article selected or excluded
2009, Orr et al.[4]	Yes	Yes	Yes	Selected
2009, Noronha et al.[23]	Polysomnography performed once	One pH measurement	No	Excluded
2008, Suurna et al.[24]	No	No	Yes	Excluded
2008, Shaheen et al.[25]	No	Yes	Yes	Excluded
2008, Sebaté et al.[26]	Polysomnography performed once	One pH measurement	No	Excluded
2008, Watson et al.[27]	Polysomnography performed once	No	No	Excluded
2007, Friedman et al.[22]	Yes	Yes	Yes	Selected
2007, Friedman et al.[28]	No	Yes	No	Excluded
2007, Dickman et al.[29]	Polysomnography performed once	One pH measurement	No	Excluded
2006, Bortolotti et al.[30]	No	No	Yes	Excluded
2006, Hawylkiewicz et al.[31]	Polysomnography performed once	One pH measurement	No	Excluded
2006, Tawk et al.[32]	No	Yes	No	Excluded
2005, Orr et al.[33]	Yes	Yes	Medication was used for only one week	Excluded
2005, Kim et al.[34]	Polysomnography performed once	No	No	Excluded
2004, Wasilewska et al.[35]	Polysomnography performed once	One pH measurement	No	Excluded
2004, Steward[36]	Yes	No	Yes	Excluded
2004, Steward[37]	Yes	No	No	Excluded
2004, Morse et al.[38]	Polysomnography performed once	No	No	Excluded
2003, Ozturk et al.[39]	Polysomnography performed once	One pH measurement	No	Excluded
2002, Konermann et al.[10]	Yes	Yes	Yes CPAP was also used	Excluded
2001, Senior et al.[40]	Yes	No	Yes	Excluded
2000, Ing et al.[20]	Yes	Yes	Yes	Selected
1999, Konermann et al.[41]	Done prior to treatment	Done prior to treatment	Yes	Excluded
1999, Xiao et al.[42]	Yes	Yes	No, cisapride was used	Excluded Chinese article

polysomnograms were treated with a proton pump inhibitor (esomeprazole magnesium, 40 mg once daily) for 2 to 6 months and then retested and reevaluated forassessment of both subjective and objective changes[22].

Ing et al.[20], 2003, selected 12 patients with OSA and GERD to participate in a placebo controlled randomised clinical trial. All patients having screening polysomnography for OSA in their laboratory (Compumedics S Series Sleep System V4.0) also underwent distal esophageal pH monitoring[20]. All polysomnographic studies were analyzed manually with AHI determined. Subjects were used as controls if the AHI was < 5. Subjects were defined as having OSA if the AHI was > 15. All apneas, hypopneas, and arousals were analyzed manually to determine their relationship to any refluxevents[20]. Patients with OSA and proven esophageal reflux were randomized to a 1-month trial of either nizatidine 150 mg po twice daily or placebo. Repeat polysomnographic study and distal esophageal pH monitoring were then performed after the nizatidine or placebo treatmentperiod[20].

The studies selected for inclusion in this review were comparative clinical trials involving patients with GERD with obstructive sleep apnea. All of the patients in the eligible studies underwent both polysomnography and esophagus pH measurements before and after drug treatment. A total of 60 patients (55% male) were evaluated. The pH measurements were obtained with either 24-hour esophageal pH analysis or transnasal wireless 24-hour pH monitoring. The medications esomeprazole and rabeprazole were used for at least 2 months. In the Friedman et al.[22] study, there was a significant tendency toward improvement in the apnea-hypopnea index (AHI) with drug treatment, while Orr et al.[4] did not report a statistically significant trend.

The general characteristics of the selected studies are shown in Table 3. One of the limitations of the studies included in this systematic review was a lack of control groups, with the exception of Ing et al.[20], which included 41 controls and 63 patients with OSA. A total of 12 patients diagnosed with GERD were selected and randomly assigned to two groups of 6 patients each that underwent treatment with nizatidine (150 mg, twice daily) or a placebo for 1 month. However, for the purpose of this review, only the nizatidine-treated group was included.

In this systematic review, we did not find a statistically significant difference between the average rate of apnea and hypopnea before and after drug treatment and the average length of time to GER before and after drug treatment (as shown in Figure 2).

Table 3. Study design and outcome.

Author	Publication Year	Study Design	Study final N	Outcomes
2009	Orr et al.	Prospective clinical trial	25 patients	GERD treatment can improve obstructive sleep apnea syndrome
2007	Friedman et al.	Prospective clinical trial	29 patients	GERD treatment can improve obstructive sleep apnea syndrome
2000	Ing et al.	Placebo controlled randomized clinical trial	12 patients	GERD treatment can improve obstructive sleep apnea syndrome

DISCUSSION

An ideal study evaluating the effets ofthe clinical treatment of GERD on obstructive sleep apneashould gather information on the potential benefits and risks of various interventions to fully assess the net comparative benefits. Interventions should be relatively inexpensive and enable the treatment of patients early in the disease process. All of the patients in these studies were seeking treatment for snoring and other symptoms of sleep apnea, and the minimum duration of treatment was as short as 2 months. It is possible that more improvement to the OSA symptoms in patients might have occurred as a result of a longer term study[22].

In reviewing the effects of clinically treating GERD on obstructive sleep apnea, we found a paucity of evidence on which to base standards of practice recommendations. Most of the data were drawn from small case series of selected patients. Although significant improvements in the AHI were reported in several of the small series, the efficacy was attributed in part to the limitations of the study, such as not including a placebo-controlled arm.

We observed that clinically treating GERD reduced the apnea-hypopnea index, but that the trend was not statistically significant. One possible explanation for the lack of statistically significant differences may be related to the relatively small sample sizes in each study. The population in this systematic review was restricted to only 66 patients. One of the mechanisms that has been postulated to explain the trend toward improvement of OSA symptoms using medication to control GERD is that esophageal acid reflux stimulates the vagus nerve and causes bronchoconstriction, which can lead to OSA[43]. Using magnetic resonance imaging, Schwab et al.[44] observed that patients with OSA have a smaller pharynx, with laterolateral narrowing and an altered shape that is circular instead of laterolaterally elliptical[34]. This anatomical variation may be related to the manifestations of GERD[4]. The direct effect of gastric contents on the laryngeal mucosa may induce symptoms suggestive of obstructive sleep apnea due to inflammation and consequent swelling of the laryngeal structures[4]. However, healthy adults have very few episodes of nocturnal GER. Freidin et al.[45] observed that patients who were diagnosed with reflux disease have more nocturnal reflux episodes than controls, and it has been observed that patients with symptoms during the day tend to had more reflux events during the night compared to healthy individuals. The increase in reflux episodes is related to an increased frequency in transient relaxation of the lower esophageal sphincter. In patients with GERD, nocturnal reflux episodes, that occur when the patient is asleep are clinically important because they are more prolonged than the episodes that occur during the day. This finding may be related to the reduced motility of the esophagus during the night and because esophageal clearance in the supine position is less efficient[45]. Ing et al.[20], 2000, showed thatnizatidine had no significant effect on AHI or minimum oxygen saturation when compared with baseline (pretreatment) parameters, but that the arousal index was significantly reduced. There were no changes in any of the OSA parameters in the placebo group. Patients receiving nizatidine had a lower AHI after therapy compared to the placebo group, but this parameter was not matched at the baseline. In another therapeutic study, patients with OSA and confirmed esophageal reflux selected from the initial study were[46] randomised in a 1-month trial with nizatidine 150 mg twice daily or a placebo. The authors reported that nizatidine reduced arousals, but not the AHI, compared with the baseline, in patients who received active therapy[20]. Compared with the placebo group, patients who were treated with nizatidine had a significantly lower RDI and number of arousals arousals after the treatment period. Ing et al.[20], implied that acid esophageal reflux may contribute to the pathogenesis of arousals and excessive daytime somnolence in patients with OSA. The effect of nizatidine on AHI and apneas is equivocal, and larger studies are necessary. The authors concluded that the use of proton pump inhibitors may assist in determining the true effects of antireflux therapy on the AHI in patients with OSA, and that studies with more participants would allow improved matching of the placebo group to the active treatment group, particularly for measuring the AHI[20].

The present study shows that the total acid GER time was reduced after medical treatment, which was consistent in all of the studies. Each of the studies used an objective evaluation of acid GER and showed improvement after treatment. The pathophysiology that links OSA to increased esophageal acid reflux contact and increased upper airway obstruction in patients with OSA remains unknown[4]. It has been postulated that a significant increase in intrathoracic negative pressure due to obstruction of the upper airways may predispose patients to the retrograde movement of the gastric contents[4] due to an increase in transdiaphragmatic pressure and increased phrenoesophageal ligament (connects the diaphragm to the lower esophageal sphincter) tension during an obstructive episode[22]. When the force exerted on the lower esophageal sphincter exceeds the closure limit, the sphincter can open and allow the passage of gastric contents through the esophagus. Penzel et al.[47] evaluated 15 patients and showed a mean AHI of 30.1 (events per hour of sleep) using polysomnography, and pH monitoring revealed that all of the patients had episodes of reflux[48,49]. Another study showed that 71.4% of patients with OSA had GER as measured using pH monitoring, while 10.4% of the cases were asymptomatic[50].

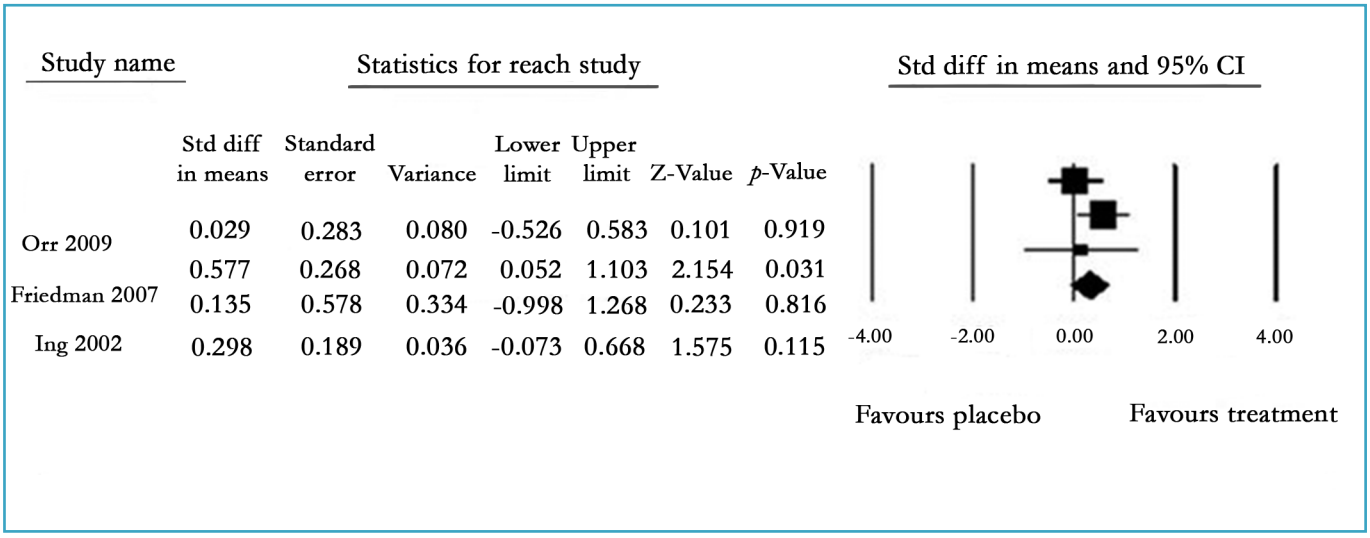

Figure 2. Comparison between the average rate of apnea and hypopnea before and after drug treatment.

In 94 patients with high Epworth Scale score who complained of excessive sleepiness, Guda et al.[6] (2004) observed that the AHI was significantly higher in patients with GER using polysomnography and pH monitoring (34.1 vs. 59.0; $p = 0.04$). The authors suggested that patients with GER have more apnea episodes than those without reflux symptoms. In another study, Ing et al.[20] selected 14 patients with OSA (diagnosed by polysomnography) and GER (diagnosed by pH monitoring) and treated them with nasal continuous positive airway pressure (nCPAP). The authors repeated the tests and observed that nCPAP reduced the AHI and GER parameters (i.e., the number of reflux events, percentage of time with pH < 4, and esophageal clearance). In the same study, 12 additional patients with OSA and GER were treated with nizatidine and a placebo. Nizatidine reduced both the OSA and acid GER parameters, while the placebo had no effect on the parameters when compared with the initial values. In 2002, Valipour et al.[51] selected 271 individuals with suspected sleep-disordered breathing to complete questionnaires related to GERD and polysomnography studies. A total of 228 individuals were included in the final statistical analysis. The authors found that the odds ratio for GERD in individuals without OSA who snored compared with those with OSA was 1.21% (95% CI, 0.7-21; $p = 0.74$) and observed that patients who snored used medication more frequently to control GERD than the patients with OSA (OR: 0.98; 95% CI; 0.8-1.1; $p = 0.70$). No differences were observed in the number of GER episodes experienced by the individuals included in the study, with apnea or snoring (62.8% vs. 41.4%; $p = 0.013$)[51].

The findings in this systematic review point to the limitations of the studies that have been published and emphasise that little is known about the impact of GERD treatment on OSA. For example, in the literature studied, only one randomised clinical trial study evaluated the relationship between obstructive sleep apnea and GERD and the effect of GERD treatment on OSA. It was not possible to compare the group that received treatment with a placebo group in the meta-analysis, and measures were not used to assess the quality of the studies because all of the studies in this analysis were "before and after" clinical trials. This systematic review suggests that more randomised clinical trials are necessary and draws attention to the need to further investigate the hypothesis that GERD can worsen OSA and that GERD treatment can improve OSA. A better understanding of these crucial issues may have a significant impact on the effectiveness and costs of managing OSA. Jung et al.19, 2010, concluded that data on non-acidic reflux and the potential relationship with sleep n are also needed (e.g., using impedance and high resolution manometry). A better understanding of the relationship between sleep and GERD may allow clinicians to manage these patients more effectively in the future.

We identified a trend in the reduction of AHI in subjects with OSA and GERD when using medication for to treat GERD. The available evidence in the literature is insufficient to form any specific recommendations, but indicates that additional studies are needed to assess the possible role of GERD treatment with medication to control OSA.

This systematic review of the available data regardingthe possible impact of the clinical treatment of GERD on obstructive sleep apneasuggests that the published evidence is insufficient as a basis for establishing recommendations or guidelines.

CONCLUSIONS

In this systematic review evaluating the clinical treatment of GERD on obstructive sleep apnea, we have found a paucity of evidence on which to base standards of practice recommendations. Most of the data were drawn from small case series of selected patients. Although significant improvements in AHI were reported in several of the small series, the efficacy was attributed in part to careful patient selection. In light of these outcomes and the increasing interest in the treatment of obstructive sleep apnea, we suggest implementing additional trials focusing on standardising pre and post-treatment targets.

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Sleep Science

REVIEW ARTICLE

Sleep quality in patients with temporomandibular disorder: a systematic review

A qualidade do sono em pacientes com disfunção temporomandibular: uma revisão sistemática

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ABSTRACT

Temporomandibular disorder (TMD) is a generic term for a group of musculoskeletal disorders of the masticatory apparatus. Patients with TMD present with several common symptoms: mandibular function pain, articular noise, headaches, bruxism and poor and unrestful sleep. Poor sleep quality can severely harm the patient's health, as it can be an etiological or perpetuating factor in TMD patients. The aims of this systematic review were to analyze the cause and effect relationship between sleep disorders and TMD and to determine the prevalence of this relationship. Studies were selected from the MedLine, Cochrane, PubMed, LILACS and BBO databases using keywords and predefined criteria. Studies published between 1990 and 2012 were included. The methods used in the articles were qualitatively analyzed, with special attention given to cross-section and case-control studies. After the inclusion criteria were applied, only 13 articles had the necessary methodological quality to be included in this systematic review. Eight of the articles analyzed sleep quality in TMD patients using validated questionnaires, two articles analyzed their sample groups using polysomnography, and three articles used only questions to collect data regarding sleep quality. Although the cause and effect relationship between sleep disorders and TMD has not been proven, there was a considerably high prevalence for the correlation of these disorders. Additional studies that use objective methods and analyze more representative patient groups are necessary.

Keywords: pain, sleep, sleep apnea syndromes, sleep disorders, temporomandibular joint dysfunction syndrome.

RESUMO

Disfunção Temporomandibular (DTM) é um termo genérico empregado a um conjunto de desordens musculoesqueléticas do sistema mastigatório. Os pacientes com DTM relatam como sintomas comuns: dor na função mandibular, presença de ruídos articulares, cefaleia, bruxismo e uma qualidade de sono ruim. A privação do sono de qualidade pode trazer significativos danos à saúde, podendo funcionar como fator etiológico ou perpetuador em pacientes com DTM. Utilizando as bases de pesquisas MEDLINE, Cochrane, Pubmed, Lilacs e BBO foi realizada essa revisão sistemática com o objetivo de avaliar a relação de causa e efeito entre os distúrbios do sono e as DTM, e a prevalência dessa associação. Foram considerados trabalhos publicados no período compreendido entre 1990 e 2012. A avaliação qualitativa da metodologia dos artigos foi empregada, com enfoque para estudos transversais e estudos caso-controle. Após a aplicação dos critérios de inclusão, apenas 13 artigos apresentaram qualidade metodológica para compor essa revisão sistemática. Oito avaliaram a qualidade do sono em pacientes com DTM por meio de questionários validados, dois submeteram suas amostras a exame de polissonografia e três utilizaram somente perguntas. Apesar de não comprovada a relação de causa e efeito entre os distúrbios do sono e as DTM, a associação das mesmas foi encontrada e com prevalência considerável. Novos estudos que utilizem métodos objetivos e que analisem casuísticas mais representativas se fazem necessários.

Descritores: dor, sono, síndrome da disfunção da articulação temporomandibular, síndromes da apneia do sono, transtornos do sono.

INTRODUCTION

Temporomandibular disorder (TMD) is a subgroup of musculoskeletal disorders and is the most common cause of pain in the facial region aside from dental causes. The most common complaints from people with TMD are pain or discomfort in the facial region and the temporomandibular joints (TMJ) that is caused or exacerbated by mandibular function. Symptoms include limited mandibular articulation with or without deviations during mouth opening, temporomandibular joint noise (pops and cracklings), headaches and changes in sleep quality[1]. TMJ disorders are classified as joint TMDs and mainly involve problems with the condyle-articular disk complex and structural incompatibilities of the joint surfaces. Disorders affecting the masticatory muscles are classified as muscular TMDs, of which myofascial pain syndrome is the main example[1].

It is estimated that 50% to 80% of the population has at least one sign or symptom of TMD. Almost 10% of individuals affected by TMD require treatment, as the disorder can cause severe functional limitations (the inability to chew and a limited ability to open one's mouth, for example) and an inability to work or participate in social activities[2]. Women aged 20

Study carried out at Universidade Federal do Paraná.
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to 50 years are five times more likely to present with TMD[2,3]. Our current understanding is that TMDs are clinical conditions with multifactorial etiologies, as one or more factors can contribute to their onset or continuation. These factors include anatomic changes, macrotrauma, microtrauma, occlusal imbalances, parafunctional habits and systemic conditions, such as emotional stress. How these factors interact and cause a TMD in each individual is still unknown[1,4]. In addition to mandibular function pain, TMD patients commonly report joint noise, headaches, bruxism and poor, unrestful sleep[2,5].

Sleep, the opposite of wakefulness, is essential for health because the body physically renews during sleep, thus protecting human beings from the natural wear that occurs when they are awake. Every human being needs to sleep for several hours within a 24 hour span. This need is met not only by the number of hours slept but also by the quality of the sleep. A large number of cerebral and organismal functions are influenced by sleep, as the conditions of the brain during the preceding period of wakefulness are reestablished during sleep[6]. Disturbing the sleep-wake cycle results in significant harm to one's health and well-being and can even increase the risk of death in the most severe cases. Because of the consequences and incidence of disorders that affect the sleep-wake cycle, they are considered a public health problem. The most common causes of sleep problems are restricted sleep, which is usually caused by excessive work, family responsibilities, medication use or other personal factors and fragmentation, which can arise from certain medical conditions or environmental factors that harm both the quantity and quality of sleep. Changes in sleep patterns can lead to reduced cognitive function, increased reaction time, memory loss, increased irritability and metabolic, endocrine and cardiovascular changes[6]. According to data from the Epidemiologic Sleep Study (Episono), approximately 32% of the studied individuals had obstructive sleep apnea syndrome (OSAS)[7].

Previous studies have shown a prevalence of TMD among individuals with OSAS[8]. Many studies have correlated poor sleep quality with chronic pain, episodes of severe pain, psychological stress and lower perceptions of self-care[9]. In addition, the prevalence of sleep disorders and TMD in the general population is high[2,10-12], suggesting that superposition of these conditions may occur frequently. In this context, a better understanding of the relationship between sleep disorders and TMD is needed. The present study seeks to evaluate the available scientific evidence regarding sleep disorders in TMD patients.

METHODS

A computer search of the MedLine, Cochrane, PubMed, LILACS and BBO databases was performed between May 20 and June 1, 2012. The following search words were used in various combinations: "temporomandibular disorders", "TMD, orofacial pain", "sleep disorders", "apnea" and "sleep quality". The initial list of articles was provided to two reviewers, who analyzed the titles and abstracts to create the final sample of studies based on the following inclusion criteria: studies that evaluated sleep quality in adult TMD patients, studies that were cross-sectional or case-control epidemiological studies and articles that were published between January 1990 and June 2012 in English, Spanish or Portuguese.

Longitudinal studies evaluating TMD or sleep disorder treatments were excluded. Both sleep disorders and TMD have many different treatments that have been described and developed in the literature. Therefore, longitudinal studies that discuss treatments could not be adequately grouped in this systematic review without introducing methodological biases that would impair comparisons between studies.

RESULTS

After the inclusion criteria were applied, 13 studies were selected. There was concordance between the reviewers for study selection. The selected studies were grouped according to the method that they used to evaluate sleep quality in TMD patients. Eight used validated questionnaires, two had patients undergo polysomnography, and three used nonstandardized questions to evaluate sleep quality in TMD patients (Figure 1). Table 1 shows 13 studies included in the final sample with their groups, evaluation methods and results.

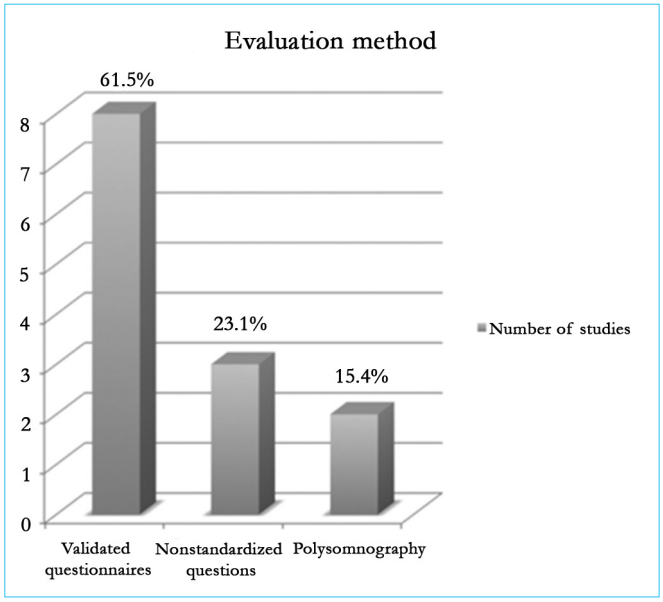

Figure 1. Methods used to evaluate sleep quality in the selected studies.

DISCUSSION

The relationship between sleep disorders and TMD patients must be investigated in a dental context based on evidence, and a critical reading of the methods used in the studies should guide discussions about the results obtained.

Sleep disorders can be diagnosed by clinical evaluation using objective and subjective measurements. Of the objective measurements, polysomnography is very important because it allows for an evaluation of the sleep architecture. It is considered the gold-standard for diagnosing most sleep disorders. Polysomnography uses various means to obtain diverse physiological measurements, such as recording the patient's electroencephalogram, electrooculogram, electromyogram, nasal airflow

Table 1. Final sample of studies and their sample groups, evaluation methods and results

Author	Sample	Evaluation Methods	Results
Hagberg et al., 1994[13]	80 TMD patients 174 members of the general population	Non standardized questions	Men with TMD had higher scores than men in the general population.
Carlson et al., 1998[14]	35 patients with jaw muscle pain 35 control patients Total = 70	Pittsburgh Sleep Quality Index	Patients experiencing pain in their masticatory muscles had more fatigue and sleep disorders than the control group did.
Yatani et al., 2002[15]	137 TMD patients	Pittsburgh Sleep Quality Index	Supports the comorbidity of reported sleep disorders, perceived pain severity stress in TMD patients.
Lindroth et al., 2002[16]	435 patients with muscular pain 139 patients with joint pain Total = 574	Pittsburgh Sleep Quality Index	The group with muscular pain had worse sleep quality than the group with joint pain did.
Vasquez-Delgado et al., 2004[17]	67 patients with daily chronic headaches, 67 with myofascial pain (MP), 67 with joint pain Total = 201	Pittsburgh Sleep Quality Index	Sleep quality was significantly worse in patients with MP than in patients in the other groups.
Selaimen et al., 2006[5]	72 TMD patients 30 controls	Sleep Analysis Questionnaire (SAQ) Beck Depression Questionnaire	Patients with TMD had high depression and sleep interruption index scores. Spontaneous pain and pain with palpation were more frequently present in the TMD patients.
Smith et al., 2009[18]	53 TMD (primary myofascial) patients	Polysomnography (PSG), Pittsburgh Sleep Quality Index, Epworth sleepiness scale	43% of TMD patients were diagnosed with two or more sleep disorders. Insomnia (36%) and sleep apnea (28.4%) were the most frequent. 75% met the self-reporting criteria for sleep bruxism, but only 17% met the PSG criteria for active sleep bruxism.
Edwards et al., 2009[19]	53 chronic TMD patients	Polysomnography and laboratory tests.	
Poveda et al., 2009[20]	850 TMD patients	Non standardized questions	Sleep disorders are among the statistically significant variables for diagnosing TMD.
Martins et al., 2010[21]	180 TMD patients	Pittsburgh Sleep Quality Index	There is a significant correlation between sleep quality and stress in individuals with TMD.
Quartana et al., 2010[22]	53 TMD patients	Insomnia Severity Index	Changes in the severity of insomnia symptoms were correlated with increased pain in TMD patients.
Davis et al., 2010[23]	251 muscular TMD patients	Non standardized questions	Significant correlation between stress, agitation and sleep problems and pain symptoms.
Porto et al., 2011[24]	81 patients with orofacial neuropathic pain 81 patients with chronic masticatory muscle pain	Pittsburgh Sleep Quality Index	Patients with neuropathic pain had more severe pain and more interference with daily life, but patients with muscular pain had more psychological problems. patients

and pulse oximetry on a polygraph. However, this test requires a location with adequate equipment and specifically trained human resources, thus requiring large financial investments and restricting the test's availability[25].

Only two of the selected studies (15.4%) used polysomnography to evaluate sleep disorders in patients. The study with the most evidence was performed by Smith et al.[18] in 2009. They analyzed patients using polysomnography and questionnaires. Forty-three percent of their patients were diagnosed with two or more sleep disorders, the most frequent of which were primary insomnia (PI; 36%) and apnea (28.4%). Some individuals experienced both problems concomitantly. Primary insomnia was associated with hyperalgesia, both in areas affected by TMD and in distinct regions (forearm), suggesting that primary insomnia could share a common underlying cause with central sensitivity and/or play a causative role in the development of hyperalgesia. Neither sleep bruxism nor sleep apnea were correlated with hyperalgesia in this study[18].

Subjective evaluation tools can be used both in the clinic and in research protocols. Some of these, such as the Sleep Disorder Questionnaire, evaluate the general aspects of sleep using quantitative and qualitative questions about sleep. Another example is the Pittsburgh Sleep Quality Index (PSQI), which provides a score for the severity and nature of the sleep disorder[25]. Other subjective instruments are more directed towards specific changes; examples include those used to evaluate excessive daytime sleepiness (EDS), such as the Epworth Sleepiness Scale[26]. For these questionnaires to have diagnostic value, they must be validated and tested in the study population[25]. They then become important tools for rapid and reliable diagnosis.

Most of the authors of the studies we selected used subjective evaluation methods. Sixty-one percent of the selected studies used validated questionnaires, and 23% of the studies used nonstandardized questions to evaluate sleep quality in patients with various TMD diagnoses. The number of studies based on patient self-reports limits the accurate determination of the real impairment of their sleep.

The Pittsburg Sleep Quality Index (PSQI) was the most commonly used scale for subjective evaluations (60%). This questionnaire has been shown to be a safe and reliable method for determining sleep quality and disturbances, and it has good test-retest reliability (r = 0.85) and internal consistency (alpha = 0.83)[27].

The results obtained in all of the studies reviewed here were similar: TMD patients had poor sleep quality independent of the evaluation method used[5,14,15,18]. There is also a consensus between the authors that the cause and effect relationship between pain and poor sleep is not known. Both pain and poor sleep appear to be part of a complex and bidirectional interaction that is not well understood. The authors focus on the possibility that sleep problems may directly contribute to central sensitization and pain amplification[18,19].

Quartana et al.[22] investigated the temporal and reciprocal relationship between insomnia and the severity of TMD pain over a month. They observed that insomnia was followed by increased pain and that treating the pain altered insomnia, but the inverse relationship was not found. The authors suggest that inflammatory molecules are released in response to sleep fragmentation and the sensitization of the nociceptors by problems in the control system. Future studies should evaluate the relationship between changes in insomnia symptoms, pain and inflammatory markers.

In a study on the role of central sensitization, Edwards et al.[19] suggested that more effective sleep and longer total sleep time were positively correlated with better diffuse noxious inhibitory control (DNIC).

Obstructive sleep apnea syndrome (OSAS) was analyzed in only one study[18]. Polysomnography tests showed that approximately one-third of the patients with TMD (28%) had OSAS. This result shows the need for systematic investigations of the occurrence of OSAS in TMD patients because of the cardiovascular effects of this sleep disorder[28,29]. However, the study did not include a matched control group to determine more clearly whether the apnea rate of 28% is in fact elevated in the TMD population. The estimated rate of sleep apnea in middle-aged adults is approximately 4% for men and 2% for women[29]. More recent studies found a 17% incidence rate for apnea in the general population, which appears to be linked to increased obesity rates[30]. Santos-Silva et al.[7] found an even higher prevalence of OSAS (approximately 32% of the studied individuals). It should also be noted that the study population in Smith et al.[18] consisted of mainly young women with relatively low body mass index (BMI) scores. Although it is unknown why sleep apnea rates would be higher in TMD populations, a recent epidemiological survey of the general population found a strong link between a diagnosis of sleep apnea and self-reported sleep bruxism[31].

The psychoemotional variables correlated with sleep disorders have been the object of several studies and were analyzed in this review. Vazquez-Delgado et al.[17] and Lindroth et al.[16] compared sleep quality and other emotional variables between patients with muscular TMD and patients with joint TMD. Both studies found similar results: patients with muscular problems had very poor sleep quality, were more stressed and had greater diurnal dysfunction. The link between stress and sleep disorders in muscular TMD patients can cause or result from the hypothalamus-pituitary-adrenal (HPA) axis and the autonomic nervous system[17].

Other studies have also investigated the connection between emotional changes (stress, anxiety, depression) and sleep quality. This review presented three case-control studies[5,13,14]. The authors of these studies found a higher incidence of emotional problems in patients with TMD. According to Selaimen et al.[5], poor sleep was a more important risk factor than depression for developing TMD. Analyzing only TMD patients, the authors found a higher prevalence of psychoemotional problems in people with poor sleep quality[15,18].

The authors unanimously agree that the management of chronic patients should include paying attention to sleep disorder complaints and referring patients with high levels of impairment to a comprehensive examination by a sleep specialist that includes polysomnography.

FINAL REMARKS

The available scientific evidence on sleep disorders and TMD was incomplete. Despite differing methodologies, the selected studies, despite different methodologies, found frequent associations between sleep disorders and TMD. Although the cause-effect relationship between pain and poor sleep is not well established, both appear to be part of a complex and bidirectional interaction that is still not well understood.

We suggest that future studies incorporate objective diagnostic methods, such as polysomnography, for sleep disorders and that validated indices, such as the RDC/TMD, be used for TMD diagnosis. This methodological rigor applied to larger sample sizes may lead to more consistent results.

Integrated management may improve sleep continuity and contribute to successful treatments for TMD and other pain disorders.

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