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New Frontier in Sleep Disorders: The Rising of an Innovative Non-invasive Neuromodulation Treatment

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ABSTRACT

Sleep is a vital physiological process essential for human health, and its deprivation can lead to various problems that negatively impact quality of life. Stress is known to worsen sleep quality. The NESA (Spanish acronym for Neuromodulación Superficial Aplicada) Non-Invasive Neuromodulation is an innovative treatment using microcurrents designed to address autonomic regulation and sleep disorders with a superficial electrotherapy treatment. This study aimed to evaluate the effectiveness of NESA in improving the sleep quality of patients with sleep disturbances. A prospective observational case series design was used. The treatment comprised ten 60-minute sessions, administered over a period of five weeks, with patients attending twice a week. Nine patients participated in the study. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), daytime sleepiness was evaluated with the Epworth Sleepiness Scale (ESS), and stress levels were quantified using the Perceived Stress Questionnaire (PSQ). Significant improvements were observed in PSQI and PSQ scores ($p=0.002$ and $p<0.001$), indicating a reduction in sleep disturbances and perceived stress. No significant changes were found in other measured variables. These results demonstrate the effectiveness of NESA in improving sleep quality and reducing stress in the participants studied.

Keywords— Neuromodulation; Physical Therapy Specialty; Sleep Quality; Stress.

INTRODUCTION

Sleep can be defined as a vital physiological phenomenon for human beings, characterized by a decrease in consciousness, reduced reactivity to external stimuli, and muscle relaxation or immobility [1]. This state can be divided into two stages: REM sleep (Rapid Eye Movement), characterized by increased sympathetic tone, and NREM sleep (Non-Rapid Eye Movement), which, in contrast, is characterized by increased parasympathetic tone [1,2]. Both states are controlled through region-specific modulation, where certain regions promote sleep while others promote arousal [3]. This process is labeled the Flip-Flop model [2,4], which involves the inhibition and stimulation between regions to prevent their coexistence, thereby allowing transitions between sleep and wakefulness [3]. Concurrently, sleep is regulated by two anatomical-functional subsystems: the homeostatic autonomic nervous system, responsible for regulating the duration, depth, and quality of sleep, and a circadian regulator, which establishes the timing for sleep during each cycle [5].

Sleep disorders significantly impact the quality of human life, causing hormonal imbalances, diseases, and even death. It is estimated that around 30% of adults and 65% of teenagers suffer from sleep disorders, leading to serious consequences such as memory and attention loss, mood disturbances, changes in reaction time, and, in some cases, heart problems [6].

It is well-established that sleep is essential for maintaining good mental and physical health. Therefore, applying treatments that improve sleep quality in patients is considered crucial [6]. Pharmacological treatments, such as sleep aids like ORAs (orexin receptor antagonists) and benzodiazepines (enhancers of the

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inhibitory neurotransmitter GABA), have shown efficacy in improving sleep parameters in patients with sleep disorders. However, the balance between the efficacy and safety of these drugs, particularly long-term tolerance, is not favorable for most medications. Concerns about long-term adverse effects and tolerability issues, as noted by Yue et al. [2023], underscore the need for safer alternatives [7]. In this context, non-invasive stimulation techniques have demonstrated effectiveness in treating neurological and mental disorders, and they have shown benefits in improving sleep quality [8,9].

Different types of neuromodulators, for example, transcranial magnetic stimulation (TMS) have shown significant improvements, not only in sleep quality, but also in some sleep disorders. Obstructive sleep apnea, restless legs syndrome, chronic primary sleep disorders or even narcolepsy are some examples of the productiveness of these methods [10–12].

Nowadays, non-invasive neuromodulation techniques, such as NESA (Spanish acronym for Neuromodulación Superficial Aplicada) technology, have shown significant results in improving sleep quality in various groups, including patients with multiple sclerosis, children with neurodevelopmental disorders, and high-performance athletes [9,13,14]. Building on these studies and utilizing this new technology, we aim to gradually improve sleep quality in “healthy” individuals without chronic or previous pathologies or disorders, other than some complications with their sleep and daily stress. By modulating the Autonomic Nervous System (ANS) and neuromodulating the retino-hypothalamic pathways [6] through NESA neuromodulation, we aim to enhance sleep quality and manage stress without the risks associated with pharmacotherapy [7].

Consequently, the purpose of this study is to analyze the effects of NESA on sleep quality in individuals with sleep disturbances. Additionally, it aims to determine if there is a correlation between the improvement of sleep quality and factors such as stress perception, alcohol consumption, stimulant substances, medications, or physical activity [15–17]. The proposed hypothesis is that NESA intervention can improve sleep quality in patients with sleep disorders.

MATERIALS AND METHODS

A. Design of the Study

This preliminary study constitutes a feasibility prospective observational investigation. A cohort of participants underwent treatment utilizing the NESA non-invasive neuromodulation technique, with assessments conducted both at the initiation and conclusion of the intervention. Inclusion criteria stipulated enrollment of subjects scoring 5 or higher on the Pittsburgh questionnaire [18,19]. Individuals presenting contraindications for NESA, including those with pacemakers, pregnant individuals, those with cancerous conditions, epilepsy, internal bleeding, compromised skin featuring ulcers or wounds, acute febrile illnesses, acute thrombophlebitis, and sensory impairments, were excluded from the treatment protocol.

1) Scope and Population: The study population consisted of individuals from the university community of University of Las Palmas de Gran Canaria who reported experiencing sleep disturbances. Participants included students, faculty, and staff members who met the inclusion criteria, which include:

- Having self-reported sleep issues, excluding those with diagnosed sleep disorders or current treatment for such conditions.

- Having a punctuation in the Pittsburgh questionnaire was higher than 5 points.

- Not having a pathology that may influence studied variables.

- Signed informed consent.

On the other hand, exclusion criteria included:

- Having contraindications for NESA microcurrents treatment: pacemaker, pregnancy, internal hemorrhage, skin with ulcers or in a bad state.

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- Electricity phobia.

Participants were selected through non-probabilistic convenience sampling, which enabled the selection of accessible individuals who voluntarily agreed to participate in the study. This sampling method was chosen to ensure ease of recruitment and to gather a willing and cooperative sample. Twenty participants from the above-mentioned university community were invited to participate in the study, and finally only 10 were included after the inclusion criteria evaluation.

Once the participants were selected, a comprehensive and systematic data collection process was initiated. The participants had to visit the Physiotherapy and Electrophysiology Laboratory of the Faculty of Health Sciences twice a week for a duration of five weeks, amounting to a total of ten sessions per participant. During these visits, a series of assessments and measurements were conducted to gather detailed data on their sleep patterns and related parameters.

B. NESA Technology

The technique is a minimally invasive non-neuromodulation treatment (NNT) designed to modulate physiological functions through electrical stimulation. It employs a low-frequency oscillating microcurrent, typically ranging from 1.3 Hz to 14.28 Hz, adjusted according to specific program requirements. The intensity of the microcurrent varies between 0.1–0.9 milliamps, while the potential difference is maintained within a range of ±3 V and ±6 V.

This treatment utilizes a sophisticated system of 25 electrodes, strategically placed on the body. Each limb is equipped with six electrodes, positioned on the wrists and ankles, respectively, allowing for simultaneous stimulation. Additionally, a directional electrode, also known as a mass electrode, complements the array. These electrodes are strategically situated along peripheral nerves with low impedance, mimicking the distribution of a glove and adapted socks for hands and feet.

The systemic effects of this approach extend beyond localized muscle or nerve activation. The coordination of impulses across the 25 electrodes, combined with the microcurrent's ultra-low electrical parameters, facilitates a comprehensive modulation of physiological responses throughout the body. This technique aims to optimize therapeutic outcomes by harnessing the body's natural electrical signaling pathways in a precise and targeted manner [20].

C. Procedure

The methodology employed in this study is outlined below, with a visual representation provided in Figure 1. This figure illustrates the programs employed, the time frame for their application, and locations of the directional electrode, which can be observed in the images on the left column.

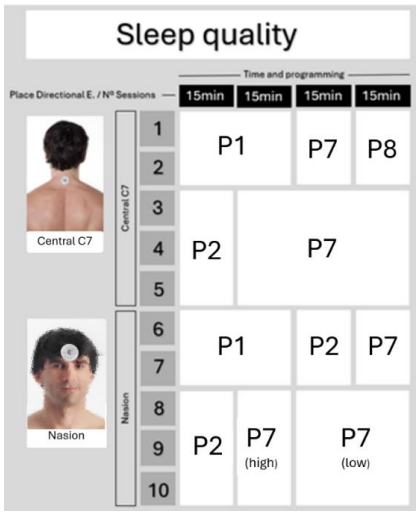

Fig.1.NESA neuromodulation protocol used in the study.

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1. Initial Phase (1st - 2nd session): In these first two sessions, the treatment is applied globally to the organism, with programs acting on the nervous system in a general manner.

- Program 1 is administered for 30 minutes, delivering frequencies ranging from 3.85 to 7.69 Hz through 24 electrodes in a sequential manner, complemented by a guiding electrode positioned at C7. This configuration ensures the initial engagement of microcurrents with the body, thereby mitigating the risk of exaggerated responses to subsequent stimuli.

- Afterward, Program 7 is employed to achieve global modulation of the Autonomic Nervous System (ANS), utilizing frequencies between 1.92 Hz and 14.29 Hz. This program generates symmetrical polarity impulses, both positive and negative, to elicit balanced responses from the ANS.

- Finally, Program 8 operates at a stable frequency of 7.69 Hz, delivering sequential stimuli of varying intensity. It targets different regions of the central nervous system with symmetrical polarity impulses in both positive and negative channels, aiming to alleviate the patient's anxiety and enhance cognitive function [21].

Throughout these sessions, the combined effects of these programs ensure a comprehensive initial engagement with the nervous system, setting the stage for more targeted interventions in subsequent phases.

2. Specific Later Phase (3rd - 4th -5th session): In this phase, the aim is to prepare the individual for sleep by modulating the hypothalamic retinohypothalamic pathways, which are essential for melatonin production.

- Program 2 is designed to enhance the flow of electrons and improve conduction within the body and is applied for 15 minutes. This program specifically targets the ventral areas of the organism, including the ventral vagus nerve, prefrontal cortex, and pineal gland. By doing so, it aims to lower the patient's level of sympathicotonia, thereby fostering the relaxation necessary to initiate sleep.

- Subsequently, Program 7 is applied for 45 minutes in the central application area. This program emphasizes vegetative modulation, a critical factor for ensuring proper progression through the phases of sleep.

The combined application of these programs in this phase ensures a comprehensive approach to preparing the individual for sleep, addressing both the physiological and neurological aspects necessary for effective sleep modulation [13,14].

3. Previous Specific Phase (6th - 7th session): In the initial phase, we position the electrode closer to the anterior part of the brain, specifically at the nasion.

- During this stage, Program 1 becomes prominent when applied for 30 minutes in a different location, at the nasion, modulating the autonomic nervous system in a manner conducive to adaptation, given that the frequencies are situated in intermediate ranges.

- Subsequently, Program 2 is implemented, targeting the ventral areas of the central nervous system to enhance the flow of electrons and conduction. This program aims to influence structures such as the suprachiasmatic nucleus, responsible for regulating the circadian rhythm.

- Lastly, Program 7, still with the electrode positioned at the nasion, the influence extends to both the prefrontal cortex and the suprachiasmatic nucleus, completing the intervention cycle in this region of the brain [21].

4. Anterior Impulse Phase (8th - 9th - 10th session): In this final stage, our focus intensifies on autonomic modulation at the nasion level, exerting a more precise influence on the central nervous system.

- Program 2 remains consistent with previous application protocols, following the established sequence of targeted areas within the central nervous system.

- Following this, Program 7 takes center stage with its prolonged application duration of 45 minutes. With the

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electrode strategically placed at the nasion, Program 7 exerts its influence on both the prefrontal cortex and the suprachiasmatic nucleus. The initial 15-minute segment of the session utilizes 6 volts (High), intensifying the treatment's impact. Subsequently, the voltage is reduced to 3 volts (Low) for the remaining 30 minutes. This modulation aims to restore equilibrium within the system and enhance the patient's adaptive response to the treatment regimen [14,20].

During the sessions, careful observation was conducted to assess the reactions of all participants. This procedure, characterized by its imperceptibility from a sensory standpoint and ease of management, was systematically monitored and documented.

D. Study Variables

The variables were measured at two time points: before the initiation of the intervention (PRE) and at the conclusion of the treatment (POST).

- Demographic variables: age, gender, place of residence, type of housing, occupation/studies, participation in sports, consumption of sleep stimulants, alcohol, drugs, medications and smoking.

- Study-specific variables, including sleep quality, sleepiness, and stress, were evaluated utilizing the following standardized scales:

- Pittsburgh Sleep Quality Index (PSQI): For the assessment of Sleep Quality. Patients responded to 19 questions, categorized into 7 components. Each component is scored on a scale ranging from 0 to 3 points, with a total score varying between 0 and 21. A PSQI score below 5 indicates the absence of sleep problems, while scores between 5 and 7 suggest the need for medical attention. Scores falling within the range of 8 to 14 indicate a requirement for medical attention and treatment, while scores exceeding 15 are indicative of severe sleep problems (18,19).
- Epworth Sleepiness Scale (ESS): The subject responds to each question on a scale of 0 (no chance of dozing) to 3 (high chance of dozing). The sum of scores ranges from 0 to 24. A score below 10 is considered normal, between 10 and 12 indicates marginal sleepiness, and above 12 indicates excessive sleepiness (22,23).
- Perceived Stress Questionnaire (PSQ): This is a 4-point Likert-type questionnaire, where 1 is "almost never" and 4 is "almost always," indicating the frequency of experiencing stress-related responses to 30 items (24). It consists of two columns, one for general responses, referring to the past year, and another for recent responses, which pertain to the last month.

E. Statistical Analysis

Statistical analyses were conducted using Jamovi version 2.3.21.0 software. Descriptive statistics were reported, including mean, median, standard deviation (±SD), minimum, and maximum values. The normality assumption for most variables was assessed using the Shapiro-Wilk test. The Wilcoxon signed-rank test was utilized for variables with non-normal distributions. Furthermore, the Friedman test was applied for variables with more than two measurements. Categorical variables were presented as frequency percentages.

F. Ethical and Legal Aspects

The study was conducted according to the principles described in the Declaration of Helsinki. The study was approved by the Research Ethics Committee with the code 2022-607-1. In addition, an informed consent form was prepared following Law 41/2002 of November 14 and was signed by each participant.

RESULTS

A. Sample

The final sample consisted of 10 patients; however, one patient was removed from the study for not completing

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all the sessions, resulting in a final sample of nine patients, of whom eight (88.9%) were female. They had a mean age of 36 years (± 17.4), with the youngest being 16 years old and the oldest being 58. Other relevant data showed that 33.3% of the subjects were students; 6 out of 9 patients engaged in some form of physical activity; 55.5% consumed some sleep-stimulating substance, with coffee being the substance of choice; finally, 66.7% consumed alcohol an average of 1.17 days per week. Significant differences were not found comparing these demographic variables.

Table I Demographic Variables Results

Variable	N (percentage)			
Gender	Female	8 (88.9%)	Male	1 (11.1%)
Occupation	Students	3 (33.3%)	Workers	6 (66.6%)
Physical Activity	Exercise	6 (66.6%)	No exercise	3 (33.3%)
Stimulating substance use	Consumed medications	5 (55.5%)	Did not consume	4 (44.4%)
Alcohol use	Consumed alcohol	6 (66.6%)	Did not consume	3 (33.3%)

B. Sleep

Significant differences were observed in the Pittsburgh results between PRE and POST evaluations (p=0.002), with a reduction of 4 points in the final score. Additionally, an increase in the maximum value was noted in one subject, indicating a deterioration in that individual's sleep quality. However, no significant differences were found in the Epworth variable between PRE and POST evaluations (p=0.170), despite a clinical decrease in scores after treatment (Table 2).

Table II Sleep Quality Results

Questionnaire	N	Mean ($\bar{x}$)	Median	SD	Min-Max	P-value
Pittsburgh PRE*	9	11.2	12	3.63	5-17	0.002
Pittsburgh POST	9	6.44	5	4.93	1-18	
Epworth PRE	9	8.44	8	6.60	0-21	0.170
Epworth POST	9	7.56	7	5.34	0-16	

* The table, developed by the authors, presents the mean, median, standard deviation, and minimum and maximum values for the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale before and after treatment. PRE refers to the initial evaluation, while POST refers to the final evaluation.

C. Stress

For the study of stress using the Perceived Stress Questionnaire (PSQ), significant differences were observed in the most recent PRE and POST measurements ($p < 0.001$), indicating improvement in the final evaluation, with the mean score decreasing by almost 10 points, as well as reductions in the minimum and maximum values. However, when considering the overall PRE and POST measurements, no significant differences were found ($p = 0.641$).

Table III Perceived Sleep Questionnaire (Psq) Results

Questionnaire	N	Mean ($\bar{x}$)	Median	SD	Min-Max	P-value
PSQ General PRE	9	71.3	70	9.07	59-84	0.641
PSQ General POST	9	73.4	76	16.1	50-97	

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PSQ Recent PRE	9	76	78	11.9	60-91	<0.001
PSQ Recent POST	9	66.2	66	10.3	50-78	

DISCUSSION

The aim of this study was to evaluate the efficacy of NESA therapy in patients with sleep disturbances as a therapeutic intervention. The results obtained align with this primary objective. Following the completion of treatment, a significant improvement in sleep quality was demonstrated using the Pittsburgh Sleep Quality Index questionnaire, with a final mean score of 6.44. Notably, 5 out of 9 patients scored below 5, indicating that they no longer experienced sleep problems post-study. Only one participant increased their score by one point. These improvements were more pronounced in patients engaged in physical activity, suggesting that it may be a favorable factor in enhancing sleep quality [15,25].

It is important to note that following the first session, patients reported increased difficulty in falling asleep and experiencing sleep disorders; however, this trend reversed after the second session, consistent with findings from other studies [13,26]. Furthermore, two subjects exhibited a significant number of vegetative symptoms after the first session, including sweating, increased urinary frequency, hypersensitivity, cold sensations, and anxiety. This study is the first to include "healthy" subjects without any diagnosed sleep problems treated using the NESA neuromodulation technique. Additionally, this is the first study to incorporate a novel directional electrode position in the nasion area, aimed at evaluating a new placement method. Future studies will be necessary to compare various placements of the directional electrode. We have thus introduced a new strategy for utilizing the directional electrode.

In addition, NESA therapy improved the perception of stress in the patients. This improvement may be attributed to enhanced sleep quality, as stress and sleep have a direct relationship, meaning that improving sleep can lead to a reduced perception of stress, and vice versa [27,28].

Although there are limited published studies on the effects of NESA on sleep quality due to its recent and innovative development, our results align with those of Garcia et al. [2022]. Their study investigated the physiological recovery of basketball players through NESA treatment and concluded that those who received this treatment experienced improved sleep quality, particularly during the REM sleep phase. Additionally, their total wake time decreased compared to the placebo group.

The results of this study can be compared with those of similar techniques for sleep treatment. In the research conducted by Wu et al. [29], the effectiveness of transcutaneous vagus nerve stimulation in the bilateral auricular concha area versus the bilateral earlobe at 20 Hz for treating sleep disorders was explored. They found that both techniques were effective, with the first group showing greater improvement. Scores on the Pittsburgh Sleep Quality Index decreased by over 50%, accompanied by reductions in anxiety and depression levels. Due to the ease of placement and the imperceptibility of NESA neuromodulation for users, this method offers a significant opportunity for comparison with placebo groups. This study is the first to employ NESA therapy in healthy subjects with sleep disturbances and stress, meaning non-diagnosed individuals.

Although, there are several limitations to consider: the study had a small and non-representative sample size due to feasibility constraints; the group was not homogeneous, making it difficult to establish differences between sexes; final measurements were taken immediately after the last session, thus the longevity of the effects needs confirmation in future studies; the Epworth Sleepiness Scale was not particularly useful, as most patients did not experience daytime sleepiness, indicating it should only be used as an inclusion criterion. Consequently, it is recommended to conduct randomized clinical trials with larger, more representative samples, including diverse age groups and both sexes, while also assessing long-term effects. Moreover, the use of objective methods such as actigraphy could provide complementary data to enhance questionnaire-based assessments.

Research involving patients with established diseases is crucial for advancing evidence in health science. However, focusing on the general population experiencing stressful situations due to work or life, which

includes sleep disturbances, presents an interesting subset of silent patients who may develop significant diseases in the future. Addressing these issues as a preventive measure is important. Recent studies in the field of sleep have demonstrated that poor sleep quality over the years can be a risk factor for developing chronic pathologies such as dementia, Alzheimer's disease, or cardiovascular problems [30].

The researcher can conclude that NESA treatment could improve the sleep quality in the subjects and that there is a correlation within the improvement in stress perception. Additionally, better results were obtained in patients who practiced physical exercise. It is recommended to expand the lines of research by conducting studies with innovative approaches to further establish the use of neuromodulation in this population.

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