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COMPARISON OF THE EFFECTS OF NERVUS VAGUS STIMULATION, TENS, AND BACKUP STIMULATION DEVICE ON THE AUTONOMIC NERVOUS SYSTEM AND PAIN IN FIBROMYALGIA PATIENTS

ABSTRACT

Purpose: This study aimed to compare the acute effects of vagus nerve stimulation (VNS), transcutaneous electrical nerve stimulation (TENS), and the backup stimulation device (Backup) on pain, sympathetic, and parasympathetic nervous system functions in fibromyalgia patients.

Methods: Thirty fibromyalgia patients (aged 20-45) from a hospital in Bursa were randomly assigned to three groups: VNS, TENS, and Backup stimulation device. Each group received a 30-minute session once weekly for five sessions. Pain was assessed using the visual analog scale (VAS), and sympathetic and parasympathetic functions were measured with the Elite heart rate variability device. Parameters included heart rate, root mean square of successive differences, proportion of NN50 divided by total RR intervals, low-frequency/high-frequency (LF/HF) power, and LF/HF ratio.

Results: No significant post-intervention changes were found in autonomic parameters across groups ($p>0.05$). However, all groups showed a significant reduction in VAS scores ($p<0.05$), indicating effective pain relief. Heart rate significantly decreased only in the Backup group ($p<0.05$), suggesting a shift toward parasympathetic dominance. Between-group analysis revealed significant differences in VAS scores between the TENS and VNS groups, and the VNS and Backup groups ($p<0.05$), indicating variability in pain response.

Conclusion: TENS, VNS, and Backup stimulation devices effectively reduce pain in fibromyalgia patients. The heart rate reduction in the Backup group suggests a potential effect on autonomic regulation, which may offer a beneficial approach for managing fibromyalgia symptoms. Although autonomic parameters showed no significant changes overall, further research is needed to understand the long-term effects and clinical relevance of these treatments.

Keywords: Autonomic nervous system, Fibromyalgia, Nervus vagus stimulation, Pain

FİBROMİYALJİ HASTALARINDA NERVUS VAGUS STİMÜLASYONU, TENS VE BACKUP CİHAZ UYARIMININ OTONOM SİNİR SİSTEMİ VE AĞRI ÜZERİNDEKİ ETKİLERİNİN KARŞILAŞTIRILMASI

ÖZ

Amaç: Bu çalışmanın amacı, vagus siniri stimülasyonu (VNS), deriden elektriksel sinir stimülasyonu (TENS) ve yedek stimülasyon cihazı (Backup) uygulamalarının fibromiyalji hastalarında ağrı, sempatik ve parasempatik sinir sistemi fonksiyonları üzerindeki akut etkilerini karşılaştırmaktır.

Yöntem: Bursa'daki bir hastaneden 20-45 yaş arasındaki 30 fibromiyalji hastası rastgele üç gruba ayrıldı: VNS, TENS ve Backup. Her grup, haftada bir 30 dakikalık seans olmak üzere beş seans aldı. Ağrı, görsel analog skala (VAS) ile değerlendirildi, sempatik ve parasempatik fonksiyonlar ise Elite kalp hızı değişkenliği cihazı ile ölçüldü. Parametreler arasında kalp atım hızı, ardışık farkların karelerinin ortalaması, NN50'nin toplam RR aralıklarına oranı, düşük frekans/yüksek frekans (DF/YF) gücü ile DF/YF oranı yer aldı.

Bulgular: Gruplar arasında otonom parametrelerde müdahale sonrası anlamlı bir değişiklik gözlemlenmedi ($p>0,05$). Ancak, tüm gruplar VAS skorlarında anlamlı bir azalma gösterdi ($p<0,05$), bu da etkin bir ağrı hafiflemesi sağlandığını göstermektedir. Kalp atım hızı yalnızca Backup grubunda anlamlı şekilde azaldı ($p<0,05$), bu da parasempatik baskınlığa doğru bir kayma olduğunu düşündürmektedir. Gruplar arası analiz, TENS ve VNS grupları ile VNS ve yedek grupları arasında VAS skorlarında anlamlı farklar buldu ($p<0,05$), bu da ağrı yanıtındaki farklılıkları vurgulamaktadır.

Sonuç: TENS, VNS ve Backup'ları fibromiyalji hastalarında ağrıyı etkili bir şekilde azaltmaktadır. Yedek grupdaki kalp atım hızı azalması, otonom düzenleme üzerinde potansiyel bir etkisi olduğunu ve fibromiyalji semptomlarının yönetimi için faydalı bir yaklaşım sunabileceğini göstermektedir. Otonom parametrelerde genel olarak anlamlı bir değişiklik gözlemlenmemiş olsa da, bu bulgular bu tedavi yöntemlerinin uzun dönem etkileri ve klinik önemi hakkında daha fazla araştırma yapılması gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Otonom sinir sistemi, Fibromiyalji, Nervus vagus uyarımı, Ağrı

INTRODUCTION

Fibromyalgia (FM) is a common chronic pain syndrome lasting at least three months and is characterized by symptoms such as hyperalgesia, allodynia, fatigue, cognitive impairment, sleep problems, and mood disorders (1). The American College of Rheumatology established the first criteria for FM diagnosis in 1990. These criteria include assessing pain in 19 different regions and calculating the Polysymptomatic Distress Scale score. An update in 2016 added a widespread pain criterion, and the scoring method was clarified (2). In 2021, the Analgesic, Anaesthetic, and Addiction Clinical Research Translations Innovations Opportunities and Networks group developed a simplified pain taxonomy for FM. According to these criteria, pain in at least 6 of 9 pain zones and moderate fatigue or sleep problems are sufficient to diagnose FM (3,4). FM occurs in 2-4% of the population and is more common in women than men. It is one of the most common causes of musculoskeletal pain in women aged 20-55 years (5).

There are widespread opinions that FM disease is caused by central nervous system dysfunction (6). The vagus nerve (VN), the tenth cranial nerve, is a complex parasympathetic nerve containing both afferent and efferent fibers (7) and plays an essential role in the neuroendocrine-immune network that ensures homeostasis (8,9). The VN integrates sensitive information and produces feedback responses by connecting with different brain regions. Studies show the effects of the VN on inflammation, mood, and pain regulation (10,11). Low vagal tone is expected in painful and inflammatory diseases such as FM, while the ventral branch of the VN is linked to emotional expression and social engagement. Therefore, the anti-inflammatory and psychological properties of the VN offer a potential therapeutic strategy in the treatment of FM (12). VN stimulation includes manual or electrotherapeutic methods that affect the VN. Animal experiments in the 1930s and 1940s showed that electrical stimulation (ES) affects brain electrical activity. The developed non-invasive method has attracted attention due to its easy applicability and minimization of potential risks. This method is applied through the external ear and is supplied by three sensory nerves (9).

VN stimulation has been shown to be an effective intervention for managing pain intensity in individuals with chronic pain (13). In a study, VN nerve stimulation was effective in pain, fatigue, and sleep disorders in people with FM (11). In a study comparing VN stimulation with diaphragmatic breathing in people with FM, the relationship between pain and change in heart rate (HR) was examined, and no significant difference was found in either group (14); another study showed that slow breathing combined with VN stimulation may be effective in pain, depression, anxiety and cardiovascular diseases (15).

Electrotherapy or ES interventions are non-invasive treatments that involve physical therapy interventions using electrical currents. ES is widely used in clinical interventions for pain relief and neuromuscular applications (16). Transcutaneous electrical nerve stimulation (TENS), a non-pharmacologic treatment, mainly involves the transmission of pulsed electrical currents across the intact surface of the skin to stimulate peripheral nerves for pain relief (17). TENS aims to stimulate low-threshold cutaneous afferents and close the pain gates to prevent the transmission of nociceptive information in the spinal cord and brainstem towards the upper centers and to relieve pain (18). In the literature, a double-blind study showed that low-frequency (LF) TENS decreased sympathetic nervous system activity and increased parasympathetic nervous system activity compared to the placebo group (19). There is also evidence that TENS can effectively reduce pain in individuals with FM in long-term applications with high or mixed frequencies, high intensity, and ten or more sessions (20). Studies have shown that TENS is effective in improving pain, disability, and quality of life in FM. It also increases pressure pain thresholds, enhances pain modulation, and, when combined with myofascial relaxation, improves cervical range of motion while reducing pain (17,21,22). Schwa Medico's BackUp system combines medium (interferential) and low frequency currents with heat to suppress pain perception and reduce pain in individuals affected by spinal problems. 80 Hz to 100 Hz applications inhibit the transmission of pain signals, while the current between 2 Hz and 15 Hz promotes the secretion of hormones that counteract pain. The combination of ES and heat has been shown to improve symptoms of chronic back pain in a study (23). The pathogenic involvement of the nervous system in FM and the numerous neurological and neuroinflammatory symptoms of this disease indicate that neuromodulatory stimulation techniques, which are effective and safe in various nervous system pathologies, can be utilized (18).

Studies have shown that TENS and VN stimulation have significant effects on the autonomic nervous system in individuals with FM (11,13-15,19,20). TENS has been widely used to manage pain and improve quality of life, while VN stimulation has been recognized for its potential in modulating autonomic function. Despite these findings, there is a lack of comparative studies evaluating the relative effectiveness of TENS and VN stimulation in FM patients. Furthermore, the Backup stimulation device, a relatively new intervention, has not yet been investigated for its effects on the autonomic nervous system or pain management in this population. This study aimed to address these gaps by comparing the effects of TENS, VN stimulation, and Backup stimulation device on pain and autonomic nervous system function in individuals with FM.

METHOD

Participants

Thirty individuals aged between 20 and 45 years with a mean age of 35.33 years who applied to the department of physical medicine and rehabilitation of a private hospital in Bursa and were diagnosed with FM by a physician were included in the study. Power and sample size calculations were conducted using G*Power version 3.1 software. To achieve a power of 0.80 with an effect size, we expected the study to be moderate, 0.50; at least ten patients in each group were required for recruitment. Participants were informed about the study's purpose, treatment duration, and the methods used during treatment. They signed the "Informed Voluntary Consent Form" prepared by the Ethics Committee standards, and permission for publication approval was obtained for the photographs to be used. The Clinical Research Ethics Committee approved the research on 06.02.2024 with the number E-10840098-202.3.02-1009 (decision no: 125).

Inclusion criteria: Participants must have a diagnosis of FM, be between the ages of 20 and 45, and have completed at least primary school education, ensuring they are literate.

Exclusion criteria: Participants will be excluded if they have a pacemaker, suffer from an orthopedic condition that prevents them from receiving treatment, or have issues with cooperation.

Study Plan

Eligible participants were provided with comprehensive explanations regarding the study methods and procedures. Following these explanations, individuals who voluntarily consented to participate and signed the informed consent form were included in the study.

Three groups were formed: vagus nerve stimulation (VNS) group (VSG), transcutaneous electrical stimulation group (TENSG), and Backup stimulation device group (BUG), consisting of a total of 30 participants who were randomly assigned based on their order of arrival. The TENSG group consisted of participants who arrived 1st, 4th, 7th, 10th, 13th, 16th, 19th, 22nd, 25th, and 28th, totaling 10 individuals. The BUG group included those who arrived 2nd, 5th, 8th, 11th, 14th, 17th, 20th, 23rd, 26th, and 29th, also comprising 10 participants. Finally, the VSG group consisted of participants who arrived 3rd, 6th, 9th, 12th, 15th, 18th, 21st, 24th, 27th, and 30th adding up to 10 participants as well. Therefore, each group contained 10 participants, ensuring an evenly distributed sample. A specialist physiotherapist treated patients allocated to the groups once a week for a total of five sessions. Since the Backup stimulation device was planned by the doctor to be used once a week, all three intervention groups received five sessions over a duration of five weeks. This schedule ensured an equitable evaluation of the treatments and allowed sufficient time for the body to recover between sessions, facilitating the monitoring of treatment effects.

VSG

The Vagustim device stimulated the ear bilaterally with electric current. Electrodes were placed on the concha and tragus parts of the ear (Figure 1). The current given was biphasic, the stimulation pulse width was 300 microseconds, and the frequency was 10 Hz. The current intensity was increased until the patient felt it, and it was applied for 20 minutes at this point (24).

TENSG

A TENS device applied a current with a frequency of 100 Hz. In the thoracic and lumbar region, self-adhesive personalized electrodes 5x5 were placed around the painful part (Figure 2), and the application was performed for 20 minutes (25).

BUG

Backup is a device that combines low frequency, medium frequency, and heat therapy. The whole spine is applied at the same time. A paper towel was laid on the device and wetted. Participants took off their clothes and lay down on the device. Exposed body parts were covered with a sheet. Calibration of the device was done specifically for each participant. The pain therapy application was selected from the device, and the current was increased until the patient felt it. Then, the pain therapy application was applied for 30 minutes (Figure 3). During the application, the participants were asked to avoid movements that would cause them to slip over the device (23).

Assessment Parameters

After the demographic information of the individuals included in the study was obtained.

Pre- and post-treatment pain assessment was measured using a visual analog scale (VAS), and the effects of treatments on the sympathetic and parasympathetic systems were measured and recorded using an Elite heart rate variability (HRV) device.

1. Demographic Information: A questionnaire was administered to gather demographic data from participants, including details such as age, gender, educational background, and body mass index (BMI).

2. Pain Assessment: Pain levels were evaluated using the VAS. This scale consists of a 10 cm line, with "0" at one end representing the absence of pain and "10" at the opposite end, signifying unbearable pain. Patients were provided with explanations regarding these endpoints and asked to mark the point on the scale that best de- described their current pain level.

3. Autonomic Nervous System Assessment: Evaluation of this system cannot be performed directly with physiologic tests. For this reason, clinical autonomic tests are usually evaluated regarding organ response to provocation of a specific physiological feature. As technology has improved, various assessment tools have been developed. New techniques such as HRV assessment and microneurography are being used. HRV analysis is based on observing R-R waves present during the resting state (26). HRV parameters are analyzed using time- and frequency-domain methods. These commonly used methods represent various ways to view the central tendency, variability, and HR distribution over time. HRV parameters consider the average values and overall magnitudes of fluctuations to quantify HR control over time. However, two individuals may have the same average R-R interval and HR responses to an event but vastly different variability of R-R intervals. The two most commonly accessible/used time-domain parameters are the standard deviation of the N-N intervals (SDNN) and the root mean square of the differences in adjacent N-N intervals (rMSSD). The SDNN represents a coarse quantification of HRV via autonomic regulation from sympathetic and parasympathetic inputs, while rMSSD represents parasympathetic activity. Unlike SDNN, rMSSD is void of HR slow-wave components, resulting in minimal respiratory influence and a more accurate representation of parasympathetic activity (27). Chen et al. (28) demonstrated the validity and reliability of Elite HRV.

The effects on the autonomic nervous system of the individuals participating in the study were measured with the Elite HRV device. The device has a finger sensor and a phone-compatible

Figure 1. Intervention of nervus vagus stimulation.

Figure 2. Intervention of TENS.
TENS: Transcutaneous Electrical Nerve Stimulation.

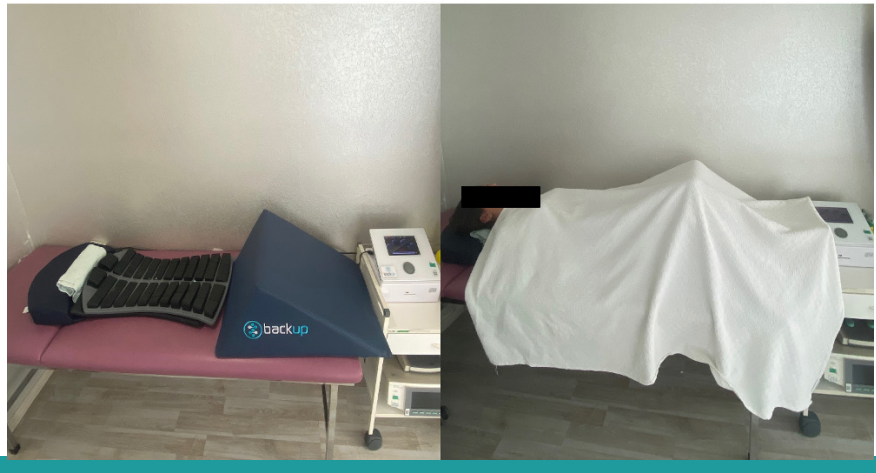

Figure 3. Intervention of Backup stimulation device.

application. The Elite HRV application is software that can synchronize with a personal monitor for instant HRV analysis by collecting R-R intervals (Figure 4). The participant breathed in and out for one minute in a sitting position under the guidance of the device, and the average of the measured values was automatically recorded in the system. The values measured with this device and their meanings are (29):

RMSSD: It is used for a snapshot of the parasympathetic branch of the autonomic nervous system and forms the basis of the HRV score.

PNN50: NN50 divided by the total number of NN (R-R) intervals.

LF power is the activity of the frequency range of 0.4-0.15 Hz. It is directly proportional to the activity of the sympathetic nervous system and represents sympathetic activity.

High-frequency (HF) Power: The frequency activity is 0.15 - 0.40 Hz. The HF band reflects parasympathetic activity and highly correlates with PNN50 and RMSSD time-domain measures.

LF/HF Ratio: The LF power to HF power ratio is commonly used to measure sympathovagal balance. It refers to the balance between opposing branches of the autonomic nervous system.

HR: It is the average value of the HR measured over one minute.

Statistical Analysis

Analyses were performed using SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM et al., USA; https://www.ibm.com/products/spss-statistics; 2017). The normality of the collected data was tested using Kolmogorov-Smirnov and Shapiro-Wilk normality tests. Descriptive statistics of the data are given as minimum, maximum, median, and mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. The one-way analysis of variance (ANOVA) method was used to compare independent groups since there were three groups. Paired-t and Wilcoxon tests were used to compare repeated measurements, such as before and after the groups, since there were two groups. Statistical analysis of categorical data between the groups was also calculated using the "chi-square test". The results obtained were considered statistically significant at $p<0.05$.

RESULT

The 30 patients who participated in the study were randomized into three groups: 10 in TENS, 10 in VNS, and 10 in Backup stimulation device (Backup). Table 1 shows the sociodemographic characteristics of the participants. Of the participants, 22 (73.3%) were female and 8 (26.6%) were male. The mean age of the participants was 35.33 years, the mean

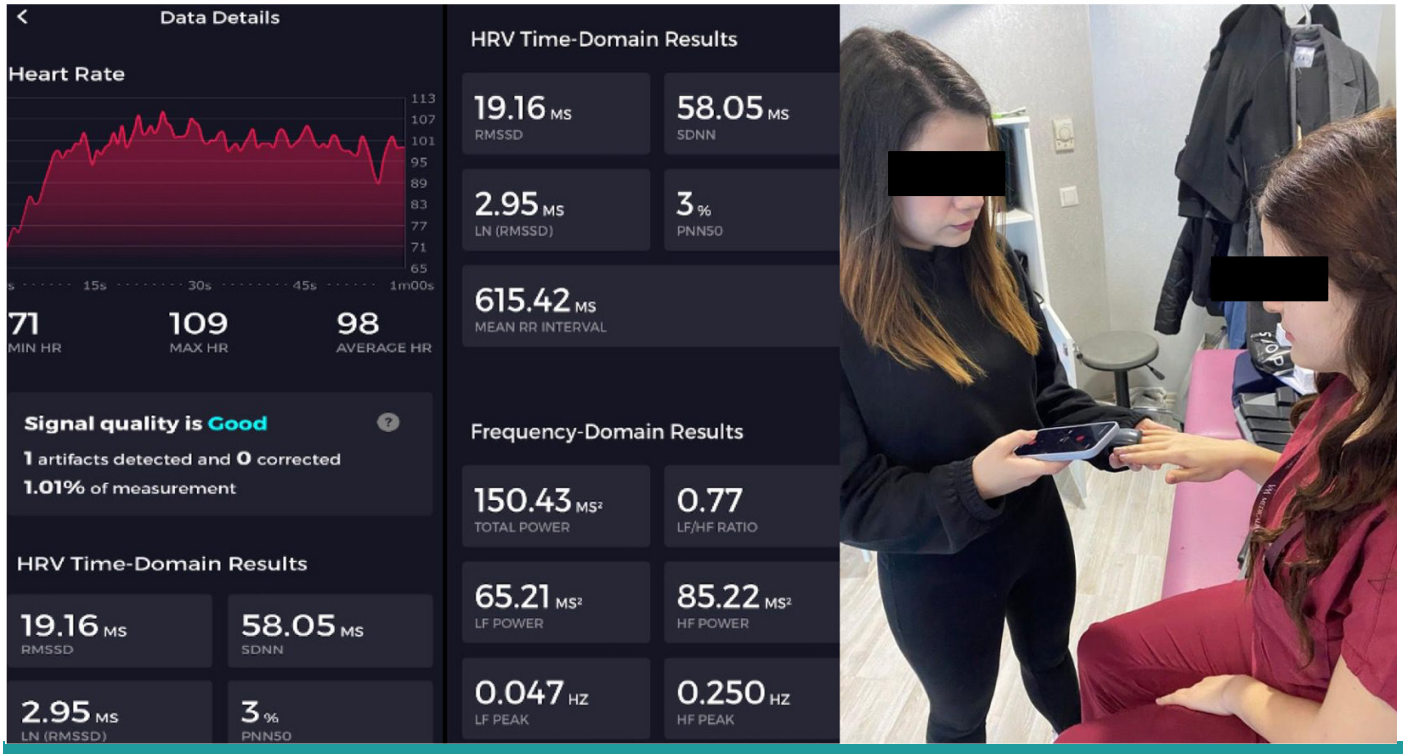

Figure 4. Elite HRV measurement and application interface.
HRV: Heart Rate Variability.

height was 167.46 cm, and the mean weight was 68.13 kg. The mean BMI was 24.42. Among the participants, 11 (36.6%) were university graduates, 11 (36.6%) were high school graduates, 2 (6.6%) were middle school graduates, and 6 (20%) were primary school graduates. There were no statistically significant differences in sociodemographic characteristics between the groups ($p>0.05$), indicating that pre-treatment values were homogeneously distributed.

The results of pre-and post-intervention evaluation in three groups are shown in Table 2. All participants completed the study. In the TENS group, an increase was observed in RMSSD and HF power values, indicating parasympathetic value, but no statistical significance was found. While there was no statistically significant difference between HR, PNN50, LF power, and LF/HF values before and after intervention ($p>0.05$), a statistically significant decrease was found in VAS value ($p<0.05$).

In the pre-and post-intervention evaluation results in VSG, a decrease was observed in RMSSD, PNN50, and HF power values reflecting parasympathetic values; however, no statistically significant difference was found. While the decrease in HR and LF/HF values before and after intervention was not statistically significant ($p>0.05$), the decrease in VAS value was statistically significant ($p<0.05$).

When the results of BUG evaluation before and after treatment were analyzed, the LF power value was analyzed, and it was observed that the sympathetic system increased before and after treatment. However, these results were not statistically significant ($p>0.05$). Similarly, there were no significant changes in RMSSD, PNN50, LF, HF power, and LF/HF values, whereas a statistically significant decrease was observed in HR and VAS values ($p<0.05$). To examine the differences among HR, RMSSD, PNN50, LF, HF, LF/HF, and VAS parameters in three groups consisting of a total of 30 patients (TENSG, VSG, and BUG), the medians of these parameters were compared using the one-way ANOVA test. When examining the statistical changes between groups, a significant difference was found in the VAS values . The analysis revealed a significant difference in the VAS parameter between at least two groups (Table 2). As shown in Table 3, according to the Wilcoxon signed-rank test, when the VAS values were analyzed between paired groups, a significant difference was observed between the TENSG and VSG groups ($p=0.000$), with the TENSG group showing a higher mean value (15.40) compared to the VSG group (5.60; $x^2=-3.804$). No significant difference was detected between the TENSG and BUG groups ($p=0.846$), as their mean values were similar (TENSG: 10.25, BUG: 10.75; $x^2=-0.994$). However, a significant difference was identified between the VSG and BUG groups ($p=0.000$), with the BUG group exhibiting a higher mean value (15.40) compared to the VSG group (5.60; $x^2=-3.822$). These findings emphasize the significant differences in VAS values, particularly between the VSG and BUG groups and the TENSG and VSG groups.

DISCUSSION

The primary findings of our study suggest that all three interventions -TENS, VNS, and Backup stimulation device- showed significant effects on both pain reduction and autonomic nervous system balance in patients with FM. Specifically, we observed a decrease in pain ($p<0.05$) and an increase in parasympathetic activity, as evidenced by changes in HRV parameters. Although statistical significance was not achieved for certain outcomes, such as HRV parameters ($p>0.05$), the general trend supports the positive impact of these treatments on the symptoms of FM, including both pain and autonomic dysfunction. The results contribute valuable insights into the potential of these non-pharmacologic interventions for managing FM (30,31).

Table 1. Sociodemographic information of participants

Groups		TENSG	VSG	BUG	p
Gender	Female	9 27%	7 (21%)	6 (18%)	0.071
	Male	1 3%	3 (9%)	4 (12%)	0.621
Age (year)		35	31.820	39.210	0.472
Height (cm)		162.42	170.33	169.71	0.788
Weight (kg)		63.82	68.47	72.22	0.821
BMI		24.04	23.52	25.26	0.231
Education status	Primary	3 (9%)	1 (3%)	2 (6%)	0.544
	Middle	1 (3%)	0	1 (3%)	0.500
	High	2 (6%)	4 (12%)	5 (15%)	0.593
	University	4 (12%)	5 (15%)	2 (6%)	0.117

TENSG: Transcutaneous Electrical Stimulation Group, VSG: Vagus Nerve Stimulation Group, BUG: Backup Group, BMI: Body Mass Index.

VNS, particularly transcutaneous VNS (tVNS), has garnered attention for its potential to influence the autonomic nervous system, particularly the parasympathetic branch. Our study found that tVNS led to a reduction in pain ($p<0.05$) and an increase in parasympathetic activity ($p>0.05$), as reflected in the HRV measurements. This finding is consistent with previous studies that have explored the role of VNS in FM and other conditions. In a study evaluating the effects of tVNS on pain in FM patients, 99 participants were assessed, and it was found that tVNS significantly improved pain scores ($p<0.05$) (32). Similarly, Kutlu et al. (9) conducted a study in which bilateral auricular tVNS combined with exercise therapy was shown to significantly reduce pain, anxiety, and depression ($p<0.05$), while also improving quality of life in FM patients. Our results are in line with these findings, as we observed positive effects on pain ($p<0.05$) and autonomic balance. However, no statistically significant change was observed in HRV parameters ($p>0.05$), which mirrors the results of a study by Paccione et

Table 2. TENS, vagus stimulation, and Backup groups intervention results

	Before median (min-max)	After median (min-max)	Intragroup analysis (p)	Inter group analysis (p)
HR				
TENSG	87.50 (75.25-99.75)	88.50 (82.20-90.25)	0.919	0.067
VSG	90 (79.5-96.5)	83.5 (78-92.5)	0.575	
BUG	86.50 (83.7-89.25)	79 (71-83.3)	**0.027***	
RMSSD				
TENSG	50.75 (37.74-67.66)	58.56 (34.35-77.09)	0.646	0.985
VSG	71.7 (33.9-99.4)	49.4 (25.4-93.1)	0.508	
BUG	44.25 (32.1-56.1)	55.50 (37.3-76)	0.241	
PNN50				
TENSG	22 (11.25-37.5)	19.50 (10.75-30)	0.445	0.791
VSG	24 (10.3-51)	14 (6.3-40.8)	0.373	
BUG	13.50 (6.7-29.7)	24.50 (12-30.3)	0.594	
LF power				
TENSG	932 (371-3218)	1094 (736-2702)	0.959	0.744
VSG	1061.7 (412.7-6242.6)	1005.8 (388.5-2566.6)	0.575	
BUG	1012.5 (424.6-2900.7)	1841 (355.3-2849.8)	0.878	
HF power				
TENSG	461.6 (303.6-1470)	629 (303-2026)	0.646	0.951
VSG	1399.7 (56.9-8510.2)	688.9 (266.3-2075.4)	0.646	
BUG	740.75 (290.5-2683.7)	587.5 (396.5-1197)	0.285	
LF/HF				
TENSG	1.99 (0.8-6.78)	1.97 (1.09-3.74)	0.799	0.897
VSG	1.8 (0.9-3.3)	1.46 (0.82-6.27)	0.878	
BUG	1.36 (0.38-3.9)	1.33 (0.83-4.3)	0.333	
VAS				
TENSG	7 (6-8)	4 (3-6)	**0.005***	**0.000****
VSG	8 (7-9)	5 (3.8-5)	**0.005***	
BUG	8 (7.75-8.25)	1 (1-1.25)	**0.004***	

*Kruskal-Wallis test $p<0.05$; **One-way ANOVA $p<0.05$, Min: Minimum, Max: Maximum, HR: Heart Rate, TENSG: Transcutaneous Electrical Stimulation Group, VSG: Vagus Nerve Stimulation Group, BUG: Backup Group, RMSSD: Root Mean Square Of The Successive Differences, PNN50: NN50 Divided by the Total Number of NN (R-R) Intervals, LF Power: Low-Frequency Power, HF Power: High-Frequency Power, VAS: Visual Analog Scale.

LF: Low-frequency, HF: High-frequency

Table 3. Inter group comparison of VAS parameters

Compared groups	n	Mean	x^2	p
TENSG - VSG	10	15.40	-3.804	**0.000***
	10	5.60		
TENSG - BUG	10	10.25	-0.994	0.846
	10	10.75		
VSG - BUG	10	5.60	-3.822	**0.000***
	10	15.40		

*Wilcoxon Signed-Rank Test $p<0.05$, N: Sample Size, x^2: Chi-Square Test, TENSG: Transcutaneous Electrical Stimulation Group, VSG: Vagus Nerve Stimulation Group, BUG: Backup Stimulation Device Group, VAS: Visual Analog Scale.

al. (14), who found no significant differences in HRV between active and placebo tVNS groups. While our study did not find statistical significance in heart rate measures ($p>0.05$), the observed changes in HRV suggest that tVNS may still play a role in modulating autonomic function in FM patients. Future studies with longer treatment periods and larger sample sizes are needed to confirm these findings and better understand the impact of VNS on FM symptoms.

TENS is widely used for managing pain in FM patients, with evidence suggesting that it can also affect autonomic nervous system activity. In our study, TENS was applied to the paravertebral region, and while we did not observe a significant decrease in heart rate ($p>0.05$), the reduction in the LF/HF ratio ($p<0.05$) suggests an increase in parasympathetic activity, aligning with findings from the existing literature. Previous studies have shown that TENS can reduce sympathetic nervous system activity and enhance parasympathetic tone, which plays a crucial role in managing stress and pain (33). For example, a study investigating TENS in hypertensive patients found that it decreased sympathetic activity while not altering blood pressure ($p>0.05$), which highlights its potential to modulate the autonomic nervous system without causing systemic changes (33). Our results suggest that TENS could be effective in managing both pain and autonomic dysregulation in FM patients. The lack of statistical significance in some outcomes ($p>0.05$) may reflect the need for longer treatment durations, larger sample sizes, or a more targeted application of TENS to better capture the effects on the autonomic nervous system.

Backup stimulation device is an emerging treatment modality that has not been widely studied in the context of FM. Our study is one of the first to investigate its effects on both pain relief ($p<0.05$) and autonomic nervous system balance ($p>0.05$). The results suggest that Backup stimulation device is effective in improving parasympathetic activation and reducing pain. Although no previous studies have specifically investigated the effects of the Backup stimulation device in FM patients, the findings from our study highlight its potential as a viable treatment option. We observed a similar increase in parasympathetic tone in the BUG ($p<0.05$) as seen in the TENS and VNS groups, with corresponding reductions in pain ($p<0.05$). This suggests that Backup stimulation device may offer similar benefits to other established treatments like TENS and VNS. The effectiveness of Backup stimulation device in improving autonomic balance and pain relief, despite its novelty, positions it as an important candidate for future research. Larger, well-controlled studies will be essential to establish the full potential of Backup stimulation device in FM management.

Our study adds to the growing body of evidence supporting the use of neuromodulatory interventions, such as TENS, VNS, and Backup stimulation device, in the treatment of FM. Previous studies have shown that FM is characterized by dysfunction of the autonomic nervous system, with increased sympathetic activity and decreased parasympathetic tone (34). For example, a study by Kutlu et al. (9) found that bilateral auricular tVNS, in combination with exercise therapy, significantly improved pain ($p<0.05$) and quality of life in FM patients, which is consistent with our findings of pain reduction ($p<0.05$) and increased parasympathetic activity. Additionally, research by Paccione et al. (14) highlighted the potential of tVNS in influencing autonomic function, though no significant changes in HRV were observed ($p>0.05$). Our study also found a decrease in the LF/HF ratio ($p<0.05$) in all three treatment groups, indicating a shift toward parasympathetic dominance, though statistical significance was not reached for all HRV parameters ($p>0.05$). This shift is consistent with studies showing that VNS and TENS can help restore autonomic balance in patients with conditions like FM (35). Our study extends this knowledge by investigating Backup stimulation device, which has shown promising results in improving autonomic function ($p<0.05$) and pain relief ($p<0.05$), but has not yet been studied extensively.

Limitations

This study has several limitations that should be acknowledged. First, the sample size was small, with only 10 participants per group, which may limit the statistical power to detect subtle differences in autonomic nervous system responses and may not

fully represent the broader population with FM. Future studies should consider a larger sample size to enhance statistical validity and generalizability. Second, the intervention duration was relatively short, limited to once-weekly sessions for five weeks. While this protocol aimed to capture initial responses, longer-term follow-up measurements would provide more insight into sustained effects and clinical applicability. Third, the study did not include a formal measure of physical activity level. Given that physical activity can influence autonomic responses, future research should incorporate this as a potential confounding factor or acknowledge it as a limitation in interpretation. Additionally, while Elite HRV was utilized for assessing HRV, details on the device's validity and reliability in clinical populations are limited. Including comprehensive device validation and exploring a range of HRV parameters would strengthen future work.

Another potential limitation is related to the Backup stimulation device. The feedback received from participants regarding the device could have influenced the outcomes. Patients' perceptions of the device and its comfort might have played a role in their response to the treatment, as this kind of neuromodulation can be affected by subjective factors such as expectations and comfort levels during the intervention. Future research should carefully control for these subjective factors and consider how they might influence the effectiveness of the Backup stimulation device.

Despite these limitations, this study provides a foundation for investigating the autonomic effects of TENS, VNS, and Backup interventions in managing FM, with implications for future research designs and larger-scale clinical trials.

CONCLUSION

The results of this study have significant implications for clinical practice. The positive effects of TENS, VNS, and Backup stimulation device on both pain ($p<0.05$) and autonomic regulation ($p>0.05$) suggest that these non-pharmacologic treatments could be valuable additions to the management of FM. Given that autonomic dysfunction is a hallmark of FM, restoring balance within the autonomic nervous system may lead to improved patient outcomes. Clinicians may consider incorporating TENS, VNS, or Backup stimulation device into their treatment protocols, depending on the patient's individual needs and response to therapy. However, as the current study was limited by sample size and treatment duration, further research with larger sample sizes, longer follow-up periods, and more detailed assessments of autonomic function is essential. Future studies should also explore the long-term effects of these treatments, as well as their potential to improve other quality-of-life measures in FM patients.

This study demonstrates that non-pharmacologic interventions, including TENS, VNS, and Backup stimulation device, are effective in managing pain and improving autonomic system balance in patients with FM. Although statistical significance was not reached in all outcomes, the results show promising trends in reducing pain and enhancing parasympathetic activity, which is crucial for managing FM symptoms.

These findings have important clinical implications. Given the limitations of pharmacological treatments, these non-invasive therapies offer a potential alternative or adjunct to traditional approaches. By targeting the autonomic nervous system, TENS, VNS, and Backup stimulation device can provide a more holistic solution to FM management, addressing both pain and the underlying autonomic dysfunction.

For healthcare professionals, incorporating these interventions into treatment plans could enhance patient outcomes, particularly for those who do not respond well to conventional medications. Future research should focus on larger samples and long-term effects to further assess their clinical efficacy.

Overall, this study highlights the potential of these non-invasive therapies to improve FM management, offering valuable insights for both clinical practice and future therapeutic strategies.

Ethics: The Medipol University Clinical Research Ethics Committee approved the research on 06.02.2024, with the number E-10840098-202.3.02-1009 (decision no: 125).

Informed Consent: Participants were informed about the study's purpose, treatment duration, and the methods used during treatment. They signed the "Informed Voluntary Consent Form" prepared by the Ethics Committee standards, and permission for publication approval was obtained for the photographs to be used.

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Conflict of Interest: Concept- GY, RK, EB; Design- GY, RK, EB; Supervision- GY; Materials- RK; Data Collection and/or Processing- GY, RK, EB; Analysis and/or Interpretation- GY, SK; Literature Search- GY, EB; Writing Manuscript- GY, RK, EB; Critical Review- GY.

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