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Increasing the quality of sleep and life by brain electrical stimulation in patients with painful diabetic neuropathy

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Abstract

Objective: Painful diabetic neuropathy is a major complication of chronic diabetes with a significant negative impact on the quality of sleep and quality of life in diabetic patients. This study was conducted to determine the single and combined effect of the primary motor cortex (M1) and left Dorsolateral prefrontal cortex (L- DLPFC/ F3) anodic transcranial direct current stimulation (tDCS) in improving sleep quality and quality of life in type 2 diabetes patients with neuropathic pain.

Method: The current study was a four-group double-blind randomized clinical trial. The statistical population consisted of all patients with type 2 diabetes aged 45 to 65 years, who were members of the Bonab Diabetes Association in 2022 and identified as having neuropathic pain by specialists. The research sample was 48 people selected through the purposeful sampling method and randomly assigned into three experimental groups and one sham control group. Patients in four groups received their respective interventions for 12 sessions, three times a week. The data collection was done using the Pittsburgh Sleep Quality Index (PSQI) and the 36-Item Short Form Quality of Life questionnaire (SF-36).

Results: According to the findings, only the stimulation of M1 and F3 areas was effective in improving the sleep quality of diabetic patients. In terms of increasing quality of life, the effect of combined treatment (stimulation of both M1 and F3 areas) was significantly higher than the F3 area stimulation and sham stimulation groups. Also, the observed effect remained stable until the 3-month follow-up stage.

Conclusion: According to the results of this research, neuropsychological rehabilitation through electrical stimulation of the M1 and F3 areas of the brain was supported to improve the sleep quality and the quality of life of diabetic neuropathy patients.

Keywords: Diabetic neuropathy pain, sleep quality, life quality, tDCS.

Introduction

Type 2 Diabetes is a common metabolic disorder in which high blood glucose levels occur due to insufficient insulin production or insulin resistance (Alipour, Javanmard & Mohammadi, 2019). Most diabetic patients are affected by diabetic neuropathy. Diabetic neuropathic pain (DNP) is characterized by burning, tingling, severe pain, and cutting or even electric shock sensations. Diabetic neuropathic pain is usually moderate to severe and often very severe at night, causing sleep disturbances and reducing sleep quality. These pains can be constant and accompanied by cutaneous Allodynia, which affects the patient's quality of life. It influences the ability to perform daily activities and hurts mood. This pain may cause the avoidance of recreational and social activities and may be associated with depression (Schreiber, Nones, Reis, Chichorro, & Cunha, 2015). Chronic neuropathic pain often causes significant suffering, reduced quality of life, and disability in

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patients and is a major contributor to the overall burden of disease (Doth, Hansson, Jensen & Taylor, 2010; Smith & Torrance, 2012; Alleman, Westerhout, Hensen, et al., 2015; Rice et al., 2016). Diabetic neuropathy and neuropathic pain are the most restrictive problems that occur in diabetic patients. Neuropathic pain (NP) is disabling, reduces sleep quality and quality of life, impairs professional performance, and limits the social participation of people with severe pain. Neuropathic pain is a complicated and heterogeneous condition with a negative impact on the professional, mental, and physical quality of life which is associated with high treatment costs. This pain is associated with other clinical conditions like diabetic peripheral neuropathy affecting 46% of patients suffering from diabetes mellitus (DM). Coping with NP is challenging and is associated with patients' dissatisfaction with medicine and non-medicine treatments and surgery (Souza, Carqueja & Baptista, 2016).

It has been suggested that neuropathic pain in diabetic patients causes many problems, especially depression and sleep disorders for patients (Davoudi, Taheri, Foroughi, Ahmadi, & Hashmati, 2020). Meanwhile, to have a healthy body, humans should spend one-third of their time in quality sleep (Chattu, Chattu, Burman, Spence & Pandi-Perumal, 2019). Spiegel, Knutson, Leproult, Tasali, and Cauter (2005) believe that chronic sleep loss—whether behavioral or sleep-disordered—may be a novel risk factor for weight gain, insulin resistance (IR), and type 2 diabetes. A study by McMullan, Schernhammer, Rimm, Hu, and Forman (2013) also shows that low melatonin secretion is independently associated with a high risk of developing T2DM. A study in Norway also reports that, along with obesity and hypertension, insomnia is the most important modifiable factor associated with T2DM (Munkhaugen et al., 2018).

On the other hand, according to some studies, lack of sleep is associated with several physiological changes, including increased levels of cortisol and ghrelin, decreased levels of leptin, and impaired glucose metabolism (AlDabal & BaHammam, 2011). Therefore, as Barone and Menna-Barreto (2011) also emphasize, the link between sleep and diabetes may be described as a vicious loop, where sleep disturbances contribute to the development of T2DM or exacerbate both types of diabetes. On the other hand, diabetes itself, when associated with poor metabolic control, is more associated with sleep disturbances. Therefore, this relationship seems to be bilateral. That is, diabetes and its complications reduce the quality of sleep, and on the other hand, sleep problems increase the probability of disorders such as diabetes. In this area, Chatto et al. (2019), in their article to highlight the increasing global problem of insufficient sleep and its significant impact on increasing the prevalence of diabetes mellitus, conducted extensive research in all major databases to review "insufficient sleep" and "diabetes mellitus".

According to the results, sleeping less than 6 hours and sleeping more than 9 hours negatively correlate with insulin resistance. They also suggest that the relationship between sleep disorders and diabetes is two-way because chronic sleep disorders increase the risk of developing insulin resistance, and diabetes, on the other hand, worsens sleep quality. Therefore, considering that quantitative and qualitative sleep disorders can increase the risk of insulin resistance and diabetes, sleep therapy may be helpful as a low-cost method to treat diabetes and diabetic neuropathic pain. For patients who do not want to use traditional medications for their diabetic neuropathy, there are several options. Some of these treatments are percutaneous electrical nerve stimulation, magnetic field therapy, low-intensity laser therapy, and monochromatic infrared light therapy. Each of these has shown varying degrees of effectiveness in improving outcomes associated with diabetic peripheral neuropathy. Among all non-pharmacological treatment methods, electrical nerve stimulation showed a lot of evidence affecting

neuropathic pain. Although diabetic neuropathy has no specific treatment, there are methods to help reduce the severity and progression of diabetic neuropathy and increase people's quality of life (Seebrat et al., 2015). One of the techniques used to reduce pain is the technique of electrical stimulation of the cerebral cortex.

In the early 1990s, epidural motor cortex stimulation (EMCS) decreased the refractory neuropathic pain by surgically implanting. Later, some noninvasive stimulation techniques were impressive in producing similar analgesic effects, at least by using repetitive transcranial magnetic stimulation (rTMS) targeting the primary motor cortex (M1). Following high-frequency rTMS (e.g., stimulation frequency with an amplitude of 5–20 Hz) delivered to the precentral gyrus (e.g., M1 area), it is possible to achieve an analgesic effect through modulation of several remote brain regions involved in the processing or controlling painful information. This pain reduction can last for some weeks, even longer than the stimulation time, especially in repeated sessions, which probably is related to long-term synaptic plasticity processes. Transcranial direct current stimulation (tDCS) is another form of transcranial stimulation using low-intensity electrical currents, typically delivered by a pair of large electrodes. Although the mechanism of tDCS is different from EMCS and rTMS, their target is the same, namely M1. Though the evidence for therapeutic efficacy in neuropathic pain for tDCS is less than rTMS, stimulating perspectives have been opened using home-based tDCS protocols for long-term management (Moisset & Lefaucheur, 2019).

On the other hand, as mentioned earlier, antidepressants are used for diabetic neuropathy, including tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin/norepinephrine reuptake inhibitors (Seeber et al., 2015). So it seems that tDCS antidepressant protocols could also reduce neuropathic pain. Regarding the positive effects of tDCS on the treatment of depression, Jensen, Chodroff, and Dworkin (2007) stated that painful diabetic polyneuropathy (PDPN) causes deep depression and low quality of life in diabetic patients due to constant pain affecting the quality of life of diabetic patients, and experiencing a reduction in daily activities and job loss. On the other hand, according to Vigod, Dennis, Daskalakis, et al. (2014), transcranial direct current electrical stimulation is a focal brain stimulation therapy that improves depressive symptoms during three weeks of treatment. It induces changes in brain regions involved in depression without affecting other brain regions or inducing changes in heart rate, blood pressure, or core body temperature. This technique applies a small current (1 to 2 mA) between two electrodes placed on the scalp, which induces local neural activity in the prefrontal cortex (Miranda, Lomarev & Hallett, 2006; Merzagora, Foffani, Panyavin, et al., 2010). Overall, various studies have confirmed the reduction of major depression by tDCS (Fregni, Boggio, & Santos, 2006; Brunoni, Ferrucci, Bortolomasi, & Vergari, 2011).

Therefore, according to the increasing prevalence of diabetes, and the announcement of a 30-50% prevalence of neuropathic pain in diabetic patients, which disrupts physical, mental, and social patients' performance and has harmful effects on the quality of sleep, quality of life, and overall the patients' performance, this research aimed to find non-pharmacological treatment solutions to reduce the neuropathic pain of diabetic patients by pure and combined application of two electrical brain stimulation protocols. The reason is that management of PDPN can be challenging for patients because even existing pain is often not alleviated by existing medical methods (Tesfaye, Chaturvedi, Eaton, Ward, et al., 2005).

The most significant necessity and importance of the current research was the need to identify effective treatment techniques, meanwhile simple, available, and non-invasive. In the case of finding positive results from the mentioned interventions, they can be applied as treatment and rehabilitation solutions

for diabetic patients and medical staff related to this disease to treat and empower patients and reduce the negative effects and personal, family, social, and economic damage caused by the increasing neuropathic pain of diabetes. Therefore, this study aimed to investigate the pure and combined effects of the primary motor cortex (M1) and left Dorsolateral prefrontal cortex (L- DLPFC/ F3) anodic tDCS on sleep quality and quality of life in type 2 diabetes patients with neuropathic pain.

Method

The current study is a four-group double-blind randomized clinical trial with clinical trial code IRCT20210214050363N1. In terms of the purpose, it is an applied study, and in terms of implementation, it is semi-experimental research of the type of Mixed analysis of variance- Split Plot ANOVA designs. The statistical population of the present study included all patients aged 45 to 65 years old with type 2 diabetes, members of the Bonab Diabetes Association in the spring and summer of 2022 who was diagnosed with type 2 diabetes by specialists at least five years ago and had a medical record in this association. As four groups were present in this research, according to Cohen's table (1986; quoted by Sarmad, Bazargan, & Hijazi, 2018, p. 376), and considering the alpha equal to 0.05, the effect size of 50 0/0, and selecting 12 subjects for each group, the power of the test can be 0/86, so at least 12 people with diabetes were selected for each group. Sampling was done based on the purposeful sampling method, i.e., according to the inclusion and exclusion criteria of the study and the probability of patients participating in the research, the patients with diabetes were selected to enter the study. Then, 48 patients who volunteered to participate in the research and were eligible to enter the study were selected. In this research, the randomization was of block type, and the randomized unit was a cluster. In that, patients were randomly assigned (48 people) to 4 groups (first 12 patients for group 1, then 12 patients for group 2, 12 patients for group 3, and finally 12 patients for group 4), using the command of generating random integer numbers (INT= (RAND*30) and rank function of Excel software.

Blindness is an essential condition in any clinical trial research, so this study was carried out in a double-blind way. That is, after randomly assigning patients to 4 groups, the interventions were randomly given to four groups A, B, C, and D. In this way, the names of the groups (intervention group A: stimulation of the primary motor cortex (M1), intervention group B: stimulation of the left posterior lateral prefrontal cortex (F3), intervention group C: both stimulation of the primary motor cortex (M1) and stimulation of the left posterior lateral prefrontal cortex (F3), intervention group D: Sham stimulation) were written on four pieces of paper, and the papers were folded. Then, by randomly selecting the first paper from the four, the intervention type of Group A was determined, by selecting the second paper from the remaining three ones, and the intervention type of Group B was specified, by selecting the third paper from the two remaining papers, the intervention type for group C was determined, and by the last paper, the fourth one, the type of intervention for group D was determined. During the implementation and providing the interventions, only the researcher (the second author) was aware of the settings of the instruments and the type of stimulation. In fact, in this research, diabetic patients in all four groups, clinical caregivers (the nurses and psychologist assistant to the researcher, who were outside of the room), and outcome evaluators (either at the association site or in the blood analysis laboratory), were not aware of the intervention type for each of the four groups.

The inclusion criteria of the study consisted of having type 2 diabetes, having neuropathic pain reported by specialist physicians, having at least five years of history of diabetes with the approval of specialist physicians, not receiving psychological treatments since the diagnosis of the disease, having middle school education and above, being between 45 to 65 years old, ability to participate in therapy sessions,

willingness to cooperate, and for female patients, not pregnant and breastfeeding while carrying out the program. The exclusion criteria included reluctance to continue the treatment, occurrence of great stress and severe and unexpected events at any stage of the intervention, severe nephropathy, retinopathy, and neuropathy as diagnosed by specialist physicians, suffering from acute psychological illness, having chronic diseases such as cancer or illness, other problematic medical conditions, except for diseases related to complications of diabetes or illnesses associated with diabetes, absence of more than two sessions or a gap between sessions of more than four days, taking any psychoactive drug or other drugs with psychological properties, having pacemaker with the intracardiac defibrillator, having a history of head and neck surgery, or a history of severe head trauma in the last six months.

Procedure

The pre-test stage: About one week before the intervention, the members of all four groups were pre-tested in terms of quality of sleep and quality of life with research tools.

Intervention: The members of all four groups received the interventions related to their group in 12 individual sessions of 40 minutes (every other day).

The post-test stage: The patients of all four groups were re-tested in terms of sleep quality and quality of life up to three days after the completion of treatment interventions.

One-month follow-up: The patients of all four experimental groups were tested in terms of sleep quality and quality of life in a one-month follow-up.

Three-month follow-up: The patients of all four experimental groups were tested in terms of sleep quality and quality of life in a three-month follow-up.

Content of sessions and methods of transcranial electrical stimulation

The interventions of this research were carried out using NeuroStim2. This instrument has two separate channels, which are electrically isolated from each other, and each channel can be set independently of the other to apply separate stimulations. Its safety and clinical tests have been done several times and have received the BS EN 60601-1 2014 standard. It should be noted that by using the Session Editor, which is provided as an option, the intensity and duration of the stimulation were set at the beginning of the session. In this way, for experimental group 1, for 40 minutes of anodic tDCS for the M1 area (20 minutes of left M1 stimulation and 20 minutes of right M1 stimulation) with an electric current of 2 mA, for experimental group 2, 40 minutes of anodal tDCS for the F3 region with an electric current of 2 mA, for the combined treatment group, for 20 minutes of M1 anodal tDCS and 20 minutes of F3 anodal stimulation (10 minutes of left M1 anodal stimulation, 10 minutes of right M1 anodal stimulation, 20 minutes of F3 anodal stimulation), with an electric current of 2 mA, were presented. For the sham-control group, using the Session Editor, the instrument was set in such a way that after 20 seconds of real stimulation, sham (fake) stimulation was presented. All four groups received their intervention for 12 sessions every other day.

Measurements

Pittsburgh Sleep Quality Index (PSQI): This questionnaire examines the sleep quality of people regarding in the last four weeks. This questionnaire's scoring is based on seven points scale: 1) a general description of sleep quality, 2) delay in falling asleep, 3) duration of useful sleep, 4) adequacy of sleep (based on the ratio of the duration of useful sleep to the total time spent in bed is calculated), 5) sleep disorders (measured as waking up at night), 6) morning performance (as problems caused by poor sleep experienced by the person during the day), and 7) a total score. Each scale of the questionnaire gets a score from zero to three. The scores of 0, 1, 2, and 3 on each scale indicate the normal situation, and the existence of a mild, moderate, and severe problem, respectively. The scores of the seven scale form the total score, which ranges from 0 to 21. A total score of 6 or more

means inadequate sleep quality (Ho, Lee, Chen, et al., 2013). The validity and reliability of this questionnaire were reported as 0.73 and 0.74 (Rasolzadeh et al., 2017).

36-Item Short Form quality of life questionnaire (SF-36): This questionnaire is the most popular and widely used tool for measuring the quality of life, designed by Warosherbon in 1992 in the United States. This 36-question questionnaire consists of 8 subscales and each subscale consists of 2 to 10 items. The eight subscales of this questionnaire are physical function (PF), role disturbance due to physical health (RP), role disturbance due to emotional health (RE), energy/fatigue (EF), emotional well-being (EW), social functioning (SF), Pain (P), and general health (GH). Also, from the integration of the subscales, two general subscales named physical health and mental health are obtained. In this questionnaire, a lower score indicates a lower quality of life and vice versa. In the Iranian sample, Cronbach's alpha values for the general subscales of this questionnaire were 0.65 to 0.90 (Montazeri et al., 2005). It should be noted that in this research, the overall quality of life score is obtained from the sum of the two subscales of physical health and mental health.

Ethical statement

To observe ethical principles, before starting the treatment, informed consent was obtained from the patients, the names and surnames of participants and all other information remained confidential, and the patients had the right to know the results of their tests if they wished; if they did not want to continue the sessions, or if diseases or acute stress occurred, the patients were allowed to leave the research process at each stage of the study, and the sham (control) group was placed in priority for receiving the real intervention after research. (ethical code: IR.PNU.REC.1399.132)

Results

The participant of study consisted of 48 diabetic patients with neuropathic pain. The mean and standard deviation of the age, gender distribution, and literacy of the participants in each group are presented in Table 1.

Table 1. Descriptive statistics of age, gender, literacy, and the results of one-way analysis of variance, chi-square, and Kramer's V of research variables in groups

Variable	Group M1 N=12		Group F3 N=12		Group M1+F3 N=12		Group Sham N=12		Statistic
Age	54.17±4.82		53.92±4.50		51.75±3.16		56.33±5.59		F3,44=1.99, P=0.130
Gender	frequency	percent	frequency	percent	frequency	percent	frequency	percent	X2=1.2 P= 0.753
Male	2	16.7	2	16.7	1	8.3	3	25	
Female	10	83.3	10	83.3	11	91.7	9	75	
Literacy	frequency	percent	frequency	percent	frequency	percent	frequency	percent	V=0.16 P= 0.877
Under diploma	6	50	8	66.7	5	41.7	5	41.7	
Diploma	4	33.3	3	25	4	33.3	4	33.3	
Academic	2	16.7	1	8.3	3	25	3	25	

The results of the one-way analysis of variance (ANOVA), Chi-square test (X2), and Cramer's V in Table 1 show that the compared groups are equal in terms of age, gender, and literacy variables (P>0/05). Table 2 demonstrates the mean and standard deviation of sleep quality and quality of life in different groups and stages.

Table 2. Mean and standard deviation of sleep and life quality in participants by group and stage

Variable	Group	Three-month follow-up		One-month follow-up		Post-test		Pre-test	
		M	SD	M	SD	M	SD	M	SD
Sleep quality	M1	11	2.37	7.42	2.15	8.17	3.13	7.92	2.19
	F3	10.42	2.11	7.17	2.52	7	2.76	7.17	2.21
	M1+F3	11.33	1.87	5.42	2.35	5.17	2.76	5.42	2.35
	Sham	10	2.52	9.75	2.45	9.58	2.39	9.92	2.15
Quality of life	M1	287.75	65.8	321.37	56.6	319.37	55.24	317.37	66.6
	F3	227.42	63.5	287.87	70.8	288.96	85.27	291.08	64.6
	M1+F3	262.08	67.3	362.46	61.8	370.25	47.24	390.75	61.16
	Sham	271.79	74.09	268.21	66.8	271.92	62.73	268.83	68.25

Table 2 shows a decreasing tendency in the mean scores of sleep quality (sleep problems) and an increasing tendency in the mean scores of quality of life in all three experimental groups. To investigate the significance of the observed changes, the mixed analysis of variance- Split Plot ANOVA (SPANOVA) was used. Before performing variance analysis, its important assumptions were checked. Checking the assumption of normality of the observations by performing the Shapiro-Wilk test, the distribution of the scores of the groups in sleep quality and quality of life in all four stages of pre-test, post-test, 1-month follow-up, and 3-month follow-up showed to be normal (P>0/05). The results of the M-box test confirmed the homogeneity of variance-covariance matrices for sleep quality (FM_{box}=0.86, P>0.001) and quality of life (FM_{box}=1.69, P>0.001). The results of Levine test confirmed the equality of error variances in the sleep quality pre-test ($F_{3,44}$=0.68, P=0.571), the sleep quality post-test ($F_{3,44}$=0.27e, P=0.844), 1-month follow-up of sleep quality ($F_{3,44}$=0.74, P=0.534), 3-month follow-up of sleep quality ($F_{3,44}$=0.10, P=0.957), for the pre-test of quality of life ($F_{3,44}$=0.27, P=0.847), quality of life post-test ($F_{3,44}$=0.31, P=0.815), 1-month follow-up of quality of life ($F_{3,44}$=1.41, P=0.252), and 3-month follow-up of quality of life ($F_{3,44}$=0.36, P=0.781).

In addition to the mentioned assumptions, the assumption of Sphericity is also necessary to use the univariate method. The results of Mauchly's univariate test confirmed the assumption of sphericity of the variance-covariance matrix was not established for the data of the present study (both sleep quality and life quality) (P<0/05). Therefore, according to the epsilon values that were greater than 0.75 for both sleep quality and quality of life data, the results of the Greenhouse-Geisser test were presented (Table 3)

After checking the assumptions, the results of variance analysis between and within the diverse subjects were examined with multivariate tests. According to the significance of Wilks's lambda test, sleep quality over time (F3,42=37.48, P<0.001), and over time in groups (F9,102=17.5, P<0.001) had a significant change. Quality of life also changed significantly over time (F3,42=22.18, P<0.001), and over time in groups (F9,102=86.3, P<0.001). Table 3 shows the results of the analysis of variance between and within the diverse subjects to check the sameness of the means in terms of time and the interaction of time and group.

Table 3. The results of the SPANOVA test to compare the means by time and by the interaction of time and group

Variable	Change source	Sum of squares	df	Mean of squares	F	Sig	Effect size
Sleep quality	Time	364.89	2.51	145.24	69.97**	<0.001	0.61
	Time and group interaction	153.15	7.54	20.32	9.79**	<0.001	0.40
	Error (Time and group interaction)	229.46	110.5	2.08			
Quality of life	Time	94642.84	1.95	48638.43	38.44	<0.001	0.47
	Time and group interaction	67961.21	5.84	11642.11	9.20	<0.001	0.39
	Error (Time and group interaction)	108326.57	85.6	1265.24			

**P<0/01

The values of the significance levels of the F statistic in Table 3 show that a significant change has occurred in the mean of sleep quality and quality of life over time with an error of less than one percent. Also, the time and group interaction results show that the changes in sleep quality and quality of life over time were not the same in the four groups.

Table 4 demonstrates the comparison of two groups in different stages done by post-hoc Bonferroni paired comparisons test.

Table 4 shows the difference between the two groups. As the values of significance levels show, none of the interventions have had a significant effect on improving sleep quality. Merely, stimulation of both M1 and F3 areas has been effective in improving the sleep quality of diabetic patients. In terms of increasing the quality of life, the effect of the combined treatment (stimulation of both M1 and F3

Table 4. Results of post hoc Bonferroni test to compare sleep quality and quality of life in groups

Variable	Group	Group	Mean differences	SD	Sig. level	Confidence Interval lower limit	Upper limit
Sleep Quality	M1	F3	0.69	0.87	NS	-1.71	3.08
	M1	M1+F3	1.79	0.87	NS	-0.60	4.19
	M1	Sham	-1.19	0.87	NS	-3.58	1.21
	F3	M1+F3	1.10	0.87	NS	-1.29	3.50
	F3	Sham	-1.87	0.87	NS	-4.27	0.52
	M1+F3	Sham	-2.98**	0.87	0.008	-5.38	-0.58
Quality of Life	M1	F3	37.63	24.7	NS	-30.59	105.87
	M1	M1+F3	-34.92	24.7	NS	-103.15	33.32
	M1	Sham	41.28	24.7	NS	-26.95	109.51
	F3	M1+F3	-72.55**	24.7	0.031	-140.78	-4.32
	F3	Sham	3.65	24.7	NS	-64.59	71.88
	M1+F3	Sham	76.19*	24.7	0.021	7.97	144.4

*P<0/05, **P<0/01

areas) was significantly higher than the stimulation of the F3 region of sham stimulation. In other words, to improve the sleep quality and the quality of life of diabetic patients, stimulation of both M1 and F3 areas has been effective.

To check the constancy of the effect of the provided treatments, the sleep quality and quality of life in different stages were compared two by two through the modified Bonferroni paired comparisons test (Table 5).

Table 5. Results of post hoc Bonferroni test to compare the stability of treatment effects in different stages

Variable	Stage	Stage	Mean differences	SD	Sig. level	Confidence Interval lower limit	Confidence Interval Upper limit
Sleep Quality	Pre-test	Post-test	3.25**	0.27	<0.001	2.49	4.01
	Pre-test	1-month follow-up	3.21**	0.32	<0.001	2.31	4.10
	Pre-test	3-month follow-up	3.08**	0.30	<0.001	2.25	3.91
	Post-test	1-month follow-up	-0.04	0.27	NS	-0.78	0.69
	Post-test	3-month follow-up	-0.17	0.20	NS	-0.72	0.39
	1-month follow-up	3-month follow-up	-0.125	0.23	NS	-0.76	0.51
Quality of Life	Pre-test	Post-test	-47.72**	6.65	<0.001	-66.09	-29.34
	Pre-test	1-month follow-up	-50.36**	7.10	<0.001	-69.99	-30.74
	Pre-test	3-month follow-up	-54.75**	7.66	<0.001	-75.93	-33.57
	Post-test	1-month follow-up	-2.65	3.32	NS	-11.81	6.52
	Post-test	3-month follow-up	-7.03	4.49	NS	-19.45	5.39
	1-month follow-up	3-month follow-up	-4.53	4.53	NS	-16.89	8.12

**P<0/01

According to the results presented in Table 5, both the quality of sleep and quality of life means in the post-test, 1-month follow-up, and 3-month follow-up stages have significantly decreased compared to the pre-test stage. However, there is no difference in the mean of sleep quality and quality of life in other phases (post-test, 1-month follow-up, and 3-month follow-up). It means that even up to the 3-month follow-up stage, the effect of the interventions remained. In other words, electrical stimulation of M1 and F3 brain areas has had a significant and stable impact on reducing sleep problems and increasing the quality of life of diabetic patients with neuropathic pain.

Discussion and Conclusion

This study was conducted to determine the single and combined effect of M1 and F3 anodic tDCS in improving sleep quality and quality of life in type 2 diabetes patients with neuropathic pain. The results showed that stimulation of M1 and F3 areas, in combination, significantly improves the quality of sleep and quality of life of diabetic patients with neuropathic pain. In that, the effect of these interventions was still stable three months after the end of the intervention. The study of Mohammadi et al. (1400) has also shown the effect of *Cranial electrotherapy stimulation* (CES) on improving the

sleep quality of patients with type 2 diabetes. The results of Kim et al.'s (2013) research show that in patients with painful diabetic polyneuropathy (PDPN), anodic tDCS in the primary motor cortex (M1) significantly reduced pain and pain threshold (PT) to pressure compared to sham.

Although it seemed that the reduction of neuropathic pain could lead to the improvement of sleep quality and quality of life of patients, despite the tendency to decrease the scores related to sleep problems and the tendency to increase the quality of life scores in the single stimulation groups, this decrease and increase were not significant. One of the reasons for the non-significance of the change in scores in single stimulation groups can be the high power of the test (0.86) in this study. Among the other results of the obtained results, it seems that the combined stimulation of M1 and F3 areas, in addition to reducing pain, depression, anxiety, and psychological problems in patients, solves sleep problems and increases the quality of life in patients. Indeed, part of the reduction in sleep problems and increase in quality of life in the combination group appears to be due to reduced pain and synaptic plasticity and neuronal viability in the primary motor cortex (due to anodic stimulation of the M1 region), and the Dorsolateral prefrontal cortex (DLPFC) region in anodic stimulation of the F3 region because, the DLPFC plays an important role in anxiety, depression, and unhappiness (Lang, Siebner, Ward, et al., 2005). good quality of sleep or "beauty sleep" might result in fewer psychophysiological problems (Garcia, Schütz, Lindskär, et al., 2018).

In addition, the DLPFC may be activated during painful states and ultimately, in turn, modulate structures involved in the emotional perception of pain, including the anterior cingulate cortex, insula, and amygdala (Lefaucheur, Drouot, Keravel & Nguyen, 2001). The neurobiological effects of tDCS on neuropathic pain suggest that individuals with chronic neuropathic pain may have defective intracortical inhibition (Portilla, Bravo, Miraval, Villamar, Schneider, et al., 2013), and tDCS delivery may induce several activities in the neural network such as increased glutamine, glutamate under the stimulating electrode, and restoration of defective intracortical inhibition. Because tDCS induces a continuous and weak electrical current, anodic tDCS can induce anti-neuropathic effects by altering the resting membrane potential. In other words, we can say that anodic tDCS induces depolarization of the stimulated area (Nitsche, Seeber, Frommann, Klein, Rochford, et al., 2005). Therefore, the present study supports the potential of tDCS to reduce sleep problems and improve the quality of life of diabetics with neuropathic pain.

Regarding the greater effectiveness of combined therapy, in which in addition to the M1 cortex, the F3 area was also stimulated, it should be noted that this technique had great potential in the treatment of major depression (Fregni et al., 2006; Brunoni et al., 2011). We can also point out the logic of using tDCS in the treatment of depressive disorders based on the knowledge of structural and functional abnormalities in the middle-inferior and right posterior-lateral prefrontal cortex, amygdala, and hippocampus in depressed patients. (Campbell, Mariott, Nahmias & McQueen, 2004; Hamilton, Siemer & Gottlib, 2008; Koenigs & Grafman, 2009).

On the other hand, diabetes, especially in those who suffer from its complications, such as neuropathic pain, leads to sleep problems. In this case, some evidence from epidemiological and experimental studies shows that obstructive sleep apnea (OSA) leads to glucose intolerance, which leads to T2DM (Almendros & Garcia-Rio, 2017; Utpat, Desai & Joshi, 2018). Hypoxia, sleep fragmentation, and activation of the sympathetic nervous system

are some of the pathways that play a significant role in the development of T2DM in people with sleep disorders (Doumit & Prasad, 2016). Sleep fragmentation causes increased sympathetic activity and higher levels of inflammation (Hernandez, Philippe & Jornayvaz, 2012). When a person is asleep, the parasympathetic nervous system predominates, which results in a decrease in heart rate, blood pressure, breathing rate, bowel movements, other bodily functions, body temperature, and basal metabolism. However, if sleep is often disturbed, this predominance of the parasympathetic nervous system does not occur, and the sympathetic mode increases. It leads to a higher load on the circulatory system, a higher basal metabolism, higher levels of stress hormones, and ultimately the risk of developing insulin resistance or diabetes (Ziegler & Milic, 2017).

The improvement of quality of life and sleep quality by tDCS of M1 and F3 areas can also be explained by the fact that direct current transcranial electrical stimulation (tDCS) increases cerebral energy and, in turn, decreases food intake and systemic blood glucose levels. This is probably due to the increase in phosphate content with high energy in the brain. In this area, the findings of Kistenmacher and colleagues (2015) show that tDCS can increase the high-energy phosphate content of the brain, reduce food consumption, and reduce insulin-independent blood glucose concentration.

In general, considering that diabetic neuropathy is characterized by constant pain affecting the quality of life of diabetic patients, and people who are affected by the experience of reduced daily activities and job loss, deep depression and low quality of life are observed in them (Jensen, Chodroff, & Dworkin, 2007); therefore, the management of diabetic neuropathy pain can be challenging for patients because the existing pain is often not reduced by the medical methods (Tesfaye et al., 2005).

According to the results of this research, the effectiveness of neuropsychological rehabilitation in diabetic neuropathy through brain electrical stimulation is supported because rehabilitation provides these patients with more autonomy and daily life capability, and in some cases, it is one of the motivational goals of patients and goes beyond pain relief. Therefore, the use of neuropsychological interventions used in this research is suggested to reduce diabetic neuropathic pain and improve the quality of sleep and life of patients with neuropathic pain.

And finally, the results of this study should be considered with caution because external influences such as changes in diet or lifestyle were not controlled. Also, the sleep quality and quality of life condition of participants were self-reported at all stages and there were no external objective reports about them, which can lead to subjective limitations of reports.

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