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Effectiveness of Transcranial Direct Current Stimulation and Pharmacotherapy in Pain Management in Patients with Chronic Pain

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Abstract

Background: A variety of pharmacological and nonpharmacological methods are used to treat chronic pain. Transcranial direct current stimulation (tDCS) through stimulating the central and peripheral nerves is a different and promising method for the treatment of chronic pain.

Objectives: The present study aimed to investigate the effectiveness of tDCS and pharmacotherapy in pain management in patients with chronic pain in Tehran, Iran.

Methods: The present study followed a clinical trial design. The statistical population comprised all patients with chronic pain who were referred to Pardis Multidisciplinary Pain Clinic in Tehran within 2020 - 21. A total of 60 patients willing to participate in the study were selected using convenience sampling. The participants were randomly divided into three groups, including pharmacotherapy (treatment by gabapentin with a dosage of 600 mg twice per day), tDCS, and control (n = 20 per group). The research instrument included the McGill Pain Questionnaire. The data were analyzed using repeated-measures analysis of variance with SPSS software (version 24.0).

Results: The results showed that both pharmacotherapy and tDCS interventions led to a reduction in the mean scores of pain management components, compared to the control group ($P < 0.001$). Furthermore, there was no significant difference between the effects of the two experimental groups on pain management components.

Conclusions: The tDCS and pharmacotherapy were both shown to be effective in pain management in patients with chronic pain. Therefore, in addition to pharmacotherapy, tDCS is also recommended for the treatment of chronic pain.

Keywords: Transcranial Direct Current Stimulation, Drug Therapy, Chronic Pain, Women

1. Background

Pain is an unpleasant emotional experience and feeling consisting of two emotional and sensory dimensions, which might or might not be associated with real tissue damage and is influenced by multiple cognitive, emotional, and environmental factors (1). Pain management is a crucial factor that can prevent the development or continuation of chronic pain by helping individuals adjust to the pain. Almost every patient adopts various strategies to control him/her pain, which are either adaptive or nonadaptive. The general opinion is that coping strategies change individuals' perception of pain severity and affect their ability to control or tolerate pain and consistency in daily activities (2, 3). Chronic pain is a major problem difficult to manage. In the best conditions, when an individual suffers from chronic pain for some time or even for years, disparate methods are used for pain alleviation (4, 5).

Any material or a mixture of materials used to treat, alleviate, prevent, or diagnose the abnormal physical states or symptoms caused by them and any material that reconstructs, normalizes, or changes the performance of limbs of humans or animals is called a drug. Any drug has possible side effects and complications in addition to its advantages (6, 7). Numerous individuals with chronic pain treated with analgesic drugs usually experience a type of pain called breakthrough pain. Breakthrough pain means relapse of pain. This pain might even come to patients regularly using analgesic drugs. This type of pain can occur for no reason or due to simple and unimportant incidents, such as moving a bed. Sometimes, breakthrough pain is caused on account of the wearing-off phenomenon (i.e., getting closer to the time of the next dosage) (8). However, pharmacotherapies are usually ineffective; therefore, they lead to patients' frequent visits to different physicians who adopt a mixture of different therapies and approaches for them. Kim et al. (9) reported that chronic pain comprises

two dimensions, namely sensory and emotional, which require combination pharmacotherapies using analgesic drugs.

A different and quite promising method for the treatment of depression, stress, anxiety, sleep disorders, chronic pain, and drug abuse is to increase intellectual competence and improve the cognition of transcranial direct current stimulation (tDCS) through stimulating the central and peripheral nerves (10). The tDCS is a relatively simple treatment in which a device with a small battery is used, similar to a tDCS device regarding size and appearance. However, it produces a wave of electrical currents different from the wave produced by the tDCS device (11). This is a noninvasive method, and the use of a weak alternating electrical current can cause temporary changes in the stimulation of disparate areas on the cerebral cortex proportionate to the stimulated regions and can result in significantly different biological interactions, compared to other methods (12).

Various factors, such as current intensity, stimulation location, electrode size, stimulation duration, and current polarity, can cause different effects (13). Several points should be taken into account when working with a tDCS device. When a neuron is in its normal resting state, and a negative stimulus is applied to the cell membrane, it will have a negative electrical charge on the neuron membrane. Consequently, nerve/neuron polarity will be reversed, and poking the neuron will end its polarity state and activate it. This operation occurs quite fast, and considering that tDCS has an alternating current, the polarity of the stimulated neuron will change rapidly. Then, it will be opened for another activation. The important point is that only ampere current can create the required electrical stimulation for neuronal activity. Therefore, the ampere electrical current leads to the rapid activity of neurons affected by tDCS (14, 15). According to Rintala et al. (16), tDCS is employed to alleviate chronic pain in patients with Parkinson's disease, and its effectiveness was approved. Studies show that tDCS effectively alleviates pain intensity and is associated with fewer side effects (16-19).

It appears that individuals with chronic pain cannot manage their pain, affecting their personal and professional lives, which highlights the importance and necessity of the present study. However, no study has dealt with this subject in patients with chronic pain, and there is a research gap in this area. The evaluation and explanation of tDCS's effect on pain management, such as miscellaneous pains, pain assessment, affective perception, and sensory perception of patients with chronic pain, are among the most important innovations of this study.

2. Objectives

Based on the above-mentioned background, the present study aimed to investigate the effectiveness of tDCS and pharmacotherapy in pain management in patients with chronic pain.

3. Methods

3.1. Design

The present study followed a clinical trial design (IRCT20211026052879N1), with experimental and control groups and a pretest, posttest, and follow-up.

3.2. Participants

The statistical population comprised all patients with chronic pain who were referred to Pardis Multidisciplinary Pain Clinic in Tehran, Iran, within 2020 - 21. A total of 60 patients willing to participate in the study were selected using convenience sampling. Concerning the number of groups (u = 3, α = 0.05, test power = 0.9, and effect size = 0.50), the sample size was obtained 20 for each group. After sampling, the participants were randomly assigned via casting lots in three pharmacotherapy, tDCS, and control groups. A random number table was used to randomly allocate the participants into experimental and control groups.

The inclusion criteria were suffering from chronic pain based on a specialist's diagnosis, female gender, age range of 35 - 60 years, holding at least a school completion certificate, and interest in participation in the intervention treatment. The exclusion criteria were suffering from severe psychological diseases according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) guidance, including neurodevelopmental disorders, schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, depressive disorders, anxiety disorders, sleep-wake disorders, sexual dysfunctions, gender dysphoria, disruptive, impulse-control, and conduct disorders, substance-related and addictive disorders, neurocognitive disorders, personality disorders, and paraphilic disorders, diagnosed based on the clinical interview.

3.3. Instruments

The McGill Pain Questionnaire: This questionnaire was designed by Melzack in 1975. It comprises 20 items and covers four dimensions, including sensory perceptions (items 1 - 10), affective perception (items 11 - 15), pain assessment (item 16), and miscellaneous pains (items 17 - 20). Item No. 1 was scored from 1 to 6 based on a Likert scale; items 11 and 12 were scored from 1 to 2 based on a Likert scale; items No.

2, 4, 6, 13, and 19 were scored from 1 to 3 based on a Likert scale; items No. 7, 8, 17, and 18 were scored from 1 to 4 based on a Likert scale; items No. 3, 5, 9, 14, 16, and 20 were scored from 1 to 5 based on a Likert scale. Therefore, the minimum and maximum scores in this tool were 20 and 61, respectively. Scores ranging from 20 to 40 and higher than 41 signified mild and severe pain, respectively (20). Mousavi and Golmakani (21) reported a Cronbach's alpha of 0.76 for the whole questionnaire. The Cronbach's alpha coefficient of the questionnaire was 0.78 in the present study.

Transcranial Direct Current Stimulation: The tDCS increases the delta wave (Hertz amplitude of 0.5 - 3) that increases endorphins. Therefore, it is utilized to alleviate pain and strengthen the feeling of relaxation. All the participants received the 20-minute delta-wave tDCS with a 2μA-current for 10 consecutive weeks. The anode electrode was placed on the C3 forehead area and the cathode electrode on the FP2 area. Each 20-minute session started by attaching ear clips and ended automatically after an hour. Considering that locking the device to patients is not common in clinical trials, it was also observed in the present study. After 10 weeks, the participants were not authorized to continue this treatment or any tDCS (22).

Pharmacotherapy: It included treatment by gabapentin with a dosage of 600 mg twice per day (300 mg in the morning and 300 mg at night) for 3 months (23).

3.4. Procedure

For the observation of ethical considerations, all the participants were ensured that all information obtained from the present study would be used to obtain results for a dissertation, and all the information would remain confidential for good reasons. Furthermore, the subjects were reminded that they could withdraw from the study whenever they wished. After the random assignment of the participants, in the next stage, the tools were used as pretests on the experimental and control groups. Then, the participants in the experimental group underwent pharmacotherapy and tDCS treatment, and the control group did not receive any treatment. At the end of the intervention, the participants of all three groups completed the questionnaire as the posttest stage and repeated the procedure for follow-up after 2 months. For the observation of ethical principles, the control group underwent a similar intervention after study completion.

3.5. Statistical Analyses

The data were analyzed by descriptive and inferential statistics, such as mean, standard deviation, and repeated measures analysis. The repeated measures analysis of variance was used to investigate the research hypothesis. The SPSS software (version 24.0) was used for data analysis.

4. Results

The mean age values of the participants in the pharmacotherapy, tDCS, and control groups were 46.00 $\pm$ 8.22, 46.33 $\pm$ 6.09, and 45.27 $\pm$ 7.21 years, respectively. Table 1 shows the demographic variables of the participants.

Table 2 shows the participants' mean values of pain management components (i.e., miscellaneous pains, pain assessment, affective perception, and sensory perception) in all three stages of pretest, posttest, and follow-up. According to Table 2, the mean scores of pain management components were reduced in the pharmacotherapy and tDCS groups, compared to those of the control group.

Table 3 shows the effects of groups, time, and interactive effects of group and time on each pain management component. According to Table 2, in addition to the effect of group and time, the interactive effect of group $\times$ time was significant for miscellaneous pain ($F=14.63, P< 0.001$), pain assessment ($F = 3.77$, $P = 0.008$), affective perception ($F = 5.52$, $P < 0.001$), and sensory perception of pain ($F = 8.94$, $P < 0.001$). Accordingly, when compared to the control group, the application of the independent variables had a significant effect on four components of pain management.

The results of the Bonferroni test revealed that the mean scores of the components of pain management during the posttest and follow-up stages were reduced in comparison to those of the pretest stage ($P< 0.001$). The difference between the mean scores in the posttest and follow-up stages was not significant. This finding indicated that the use of independent variables could lead to a reduction of the mean scores of pain management components, and the changes having occurred in the follow-up stage have continued. Furthermore, according to the results, when compared to the control group, both independent variables of pharmacotherapy and tDCS led to a reduction in the mean scores of pain management components. There was no significant difference between the effects of two independent variables on pain management components.

5. Discussion

The present study aimed to investigate the effectiveness of tDCS and pharmacotherapy in pain management in patients with chronic pain in Tehran, Iran. The results indicated the effectiveness of pharmacotherapy in the components of miscellaneous pains, pain assessment, affective perception, and sensory perception. The results are consistent with the results of studies performed by Kim et al. (9), Kang et al. (24), and Ngernyam et al. (25). Kang et al. (24) suggest that tDCS can result in significant pain relief in patients with fibromyalgia and might be an effective add-on

Table 1. Demographic Variables of Participants [a]

Groups	Age (y)	Education Level		Employment Status	
		High School Education	College Education	Employed	Housewife
Pharmacotherapy	46.00 ± 8.22	1 (6.67)	14 (93.33)	11 (73.33)	4 (26.67)
tDCS	46.33 ± 6.09	1 (6.67)	14 (93.33)	10 (66.67)	5 (33.33)
Control	45.27 ± 7.21	2 (13.33)	13 (86.67)	11 (73.33)	4 (26.67)
P-value	0.775	0.868		0.780	

Abbreviations: SD, standard deviation; tDCS, transcranial direct current stimulation.
[a] Values are expressed as No. (%) or mean ± SD.

Table 2. Pain Management Components in Experimental and Control Groups [a]

Variables and Phases	Pharmacotherapy	tDCS	Control	P-Value
Miscellaneous pains				
Pretest	30.33 ± 4.79	32.47 ± 3.94	30.53 ± 3.42	0.820
Posttest	23.47 ± 4.17	27.58 ± 3.48	29.07 ± 3.39	0.001
Follow-up	23.53 ± 4.34	28.20 ± 3.10	29.40 ± 4.21	0.001
Pain assessment				
Pretest	11.00 ± 2.03	11.93 ± 1.34	10.89 ± 1.62	0.738
Posttest	8.80 ± 1.82	9.62 ± 1.35	11.33 ± 2.02	0.001
Follow-up	8.60 ± 2.23	9.80 ± 1.52	11.14 ± 2.20	0.001
Affective perception				
Pretest	3.54 ± 1.25	3.60 ± 1.12	3.30 ± 1.18	0.680
Posttest	2.27 ± 0.88	2.69 ± 0.82	3.27 ± 0.87	0.001
Follow-up	2.07 ± 0.92	2.31 ± 1.09	3.49 ± 1.17	0.001
Sensory perception				
Pretest	15.81 ± 2.35	16.45 ± 2.44	16.04 ± 2.70	0.430
Posttest	12.94 ± 2.97	14.32 ± 2.23	15.88 ± 2.38	0.001
Follow-up	12.60 ± 2.80	14.56 ± 2.42	16.38 ± 2.74	0.001

Abbreviations: SD, standard deviation; tDCS, transcranial direct current stimulation.
[a] Values are expressed as mean ± SD.

treatment. Ngernyam et al. (25) observed a significant association between a decrease in pain intensity and an increase in peak theta-alpha frequency at the stimulation site in patients with neuropathic pain from spinal cord injury.

For explaining the effectiveness of pharmacotherapy in pain management, it should be stated that pharmacotherapy affects the balance of the brain's chemical matters to reduce or completely remove the symptoms of a disorder. The researchers believe that signs, symptoms, and mental experiments pertinent to psychological disorders signify the insufficient work of the central nervous system (brain) and are caused due to chemical imbalance in the brain. Any activity performed in the brain results from chemical molecules which affect, stimulate, or control neurons as neurotransmitters (26). In pharmacotherapy, drugs operate as chemical molecules or natural neurotransmitters and enhance or hinder their function or hinder their activity. Therefore, pharmacotherapy reduces or removes the symptoms of psychological disorders (27).

The results of studies indicated the effectiveness of tDCS in the components of miscellaneous pains, pain assessment, affective perception, and sensory perception. The tDCS affects pain management. The results are consistent with the results of a study conducted by Rintala et al. (16). Rintala et al. (16) reported that the use of cranial electrotherapy stimulation at home by individuals with Parkinson's disease is feasible and might be relatively helpful in decreasing pain. It uses particular frequencies from alpha brain waves to balance the natural serotonin level. The tDCS appears to strengthen the same alpha brain

Table 3. Repeated Measurement Results for the Effects of Group, Time, and Interaction of Time and Group

Variables and Source	SS	MSE	F	P	η^2
Miscellaneous pains					
Time	589.22	1156.27	10.70	< 0.001	0.34
Group	650.71	291.67	93.68	< 0.001	0.69
Time × group	375.10	539.45	14.63	< 0.001	0.41
Pain assessment					
Time	31.07	100.37	6.51	0.003	0.24
Group	30.04	124.28	10.16	< 0.001	0.19
Time × group	31.81	179.56	3.72	0.008	0.15
Affective perception					
Time	20.80	61.60	7.09	< 0.001	0.25
Group	22.50	43.53	21.71	< 0.001	0.24
Time × group	17.73	67.47	5.52	< 0.001	0.21
Sensory perception					
Time	235.39	578.93	8.54	< 0.001	0.29
Group	144.37	169.33	35.82	< 0.001	0.45
Time × group	118.96	279.47	8.94	< 0.001	0.30

Abbreviations: SS, sum of squares; MSE, mean squared error.

waves that are required for balancing the serotonin level. It regulates the blood flow between two brain hemispheres, thereby regulating the limbic system, thalamus, and basal ganglia. Therefore, the basal ganglia and thalamus regulate serotonin and alleviate chronic pain.

Additionally, tDCS changes the hormone level and neurotransmitters, which affects the neural system. The tDCS increases the activity of monoamine oxidase and the concentration of gamma-aminobutyric acid (GABA). The tDCS reduces the strength of beta waves and helps correct the abnormalities of these two waves by causing therapeutic effects (28).

According to one of the theories set forth about the effectiveness of tDCS, this stimulation functions in the amplitude of sound waves ranging from 0.5 to 100 Hz through causing intervention in the oscillations of brain waves, and this influence results from affecting the brain waves (29). The tDCS sends a mild electrical pulse and causes neurotransmitters' generation, balance, and regulation (30). The neurotransmitters, such as norepinephrine, serotonin, and GABA that influence the information process and memory, have a mediating effect on tDCS by affecting blood flow and cerebrospinal fluid (31).

The GABA is the largest and most crucial inhibitory transporter in the central nervous system (32). The neurocognitive studies have focused on glutamate stimulators and inhibitory interstitial neurons, such as GABA (33). These studies have revealed structural, functional, and neural deficiencies in both glutamate stimulators and inhibitory interstitial neurons in patients suffering from chronic pain, which can destroy the integrity of signals in the cerebral cortex and hippocampus (34).

The tDCS affects the subcortical limbic structures, hypothalamus, thalamus, brainstem, and network activators. The stimulation of these structures can lead to the increased release of neurotransmitters, such as serotonin, beta-endorphin, and norepinephrine (35). Serotonin can inhibit nociceptive and is probably crucial in the endogenous anti-pain system. The endogenous anti-pain system consists of intermediary neurons inside the dorsal horn of the spinal cord and the descending nervous pathway, which controls the transmission of pain messages. This system is activated inside by opioids and GABAergic mechanisms (36).

In this method (i.e., tDCS), a direct current is applied to the brain through the brainstem, limbic system, network activator systems, or hypothalamus. Accordingly, this affects the generation of neurotransmitters and probably the activity of the default network mode or default network and a neural network on a large scale, which includes areas with closed activities and separated from other neural networks.

5.1. Limitations

The present study was performed only on women with chronic pain in Tehran. Caution should be exercised when generalizing the results of the present study to patients suffering from other types of chronic pain or those suffering from the aforementioned diseases with psychological disorders. Gastrointestinal symptoms, dizziness, weakness and lethargy, and in some cases sleep disorders were the most important side effects of the pharmacotherapy intervention. Moreover, in some cases, itching of the electrode site and redness of the skin were the most important side effects of the tDCS intervention.

5.2. Conclusion

The results showed that tDCS and pharmacotherapy were both effective in pain management in patients with chronic pain. Therefore, physicians, nurses, and health specialists are recommended to use pharmacotherapy and tDCS for psychological empowerment, recovery acceleration, and treatment management of patients with chronic pain.

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Footnotes

Authors' Contribution: Atefeh Lotfi Jabali, study concept and design, acquisition of data, analysis, and interpretation of data, and statistical analysis; Mina Mojtabaei, administrative, technical, and material support and study supervision; Malek Mirhashemi, critical revision of the manuscript for important intellectual content.

Clinical Trial Registration Code: The present study followed a clinical trial design (IRCT20211026052879N1), with both experimental and control groups and a pretest, posttest, and follow-up.

Conflict of Interests: There is no conflict of interest to declare.

Ethical Approval: This study was approved by the Ethics Committee of Islamic Azad University, Roudehen Branch (code: 113482000598791).

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Informed Consent: The questionnaires were filled with the participants' satisfaction, and written informed consent was obtained from the participants.

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