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Case Report

Transcranial Direct Current Stimulation (tDCS) Combined with Therapeutic Exercise and Cognitive Rehabilitation to Treat a Case of Burning Mouth Syndrome (BMS) Related Pain

Francisco José Sánchez-Cuesta [1,†], Yeray González-Zamorano [2,†], Aida Arroyo-Ferrer [1], Martín Avellanal [3], Josué Fernández-Carnero [4,*] and Juan Pablo Romero [1,5,*]

1 Facultad de Ciencias Experimentales, Universidad Francisco de Vitoria, 28223 Pozuelo de Alarcón, Spain; fjose.sanchez@ufv.es (F.J.S.-C.); aida.arroyo@ufv.es (A.A.-F.)
2 Escuela Internacional de Doctorado, Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, 28933 Alcorcón, Spain; yeraygonzalezzamorano@gmail.com
3 Pain Clinic, Hospital Universitario Sanitas La Moraleja, Consultores en Dolor, 28050 Madrid, Spain; avellanalmartin@gmail.com
4 Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, 28933 Alcorcón, Spain
5 Brain Damage Unit, Beata María Ana Hospital, 28007 Madrid, Spain
* Correspondence: josue.fernandez@urjc.es (J.F.-C.); p.romero.prof@ufv.es (J.P.R.); Tel.: +34-917091400 (J.F.-C.); +34-914888949 (J.P.R.)
† Both authors contributed equally to this work.

Abstract: Burning Mouth Syndrome (BMS) is a multifactorial, chronic pain condition with neuropathic and psychogenic mechanisms. Cortical activation as well as sustained attention and executive functions have proven to be affected by chronic pain. The main objectives of this work were to test the efficacy of a multidimensional personalized pain treatment protocol and to investigate if the effects are based on psychophysical pain processing changes or cognitive effects. A 74-year-old female with 2 years of BMS received 10 sessions of a combined protocol of anodal left dorsolateral prefrontal cortex tDCS, cognitive therapy, and therapeutic exercise. The subjective perception of pain decreased by 47% after treatment but returned to the baseline at 45 days. No changes were found in objective pain measurements apart from a transient worsening of conditioned pain modulation. A large effect size was found in all functional scales, processing speed and executive control as well as sustained attention that persisted during follow-up. No changes in anxiety and depression were found. A multimodal therapeutic approach combining TDCS, cognitive rehabilitation and therapeutic exercise produces improved quality of life, disability and pain perception correlated with improvements in processing speed, executive control and sustained attention but independent of changes in psychophysical pain processing.

Keywords: TDCS; Burning Mouth Syndrome; cognitive rehabilitation; therapeutic exercise; pain rehabilitation; personalized medicine

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1. Introduction

Burning Mouth Syndrome (BMS) is an idiopathic and multifactorial condition characterized by a severely painful burning sensation of the tongue and mucosal tissue that can last from days to months. Its underlying etiology is not well understood, and it can arise as a primary syndrome after previous oral pathologies or following an infection. Interestingly, neuropsychiatric conditions such as major depression, chronic anxiety and mood disorders have been associated with BMS [1].

BMS is much more common in peri- and postmenopausal women due to the decrease of estrogenic levels leading to the atrophy of oral mucosal tissue, leaving this area more susceptible to inflammatory changes [2].

Treatment is not always effective and includes antidepressants, benzodiazepines and neuroleptics—drugs which are not without adverse cognitive side effects considering that older adults are the population that most frequently suffer from BMS and thus have greater vulnerability to these side effects [3].

Cortex stimulation has been increasingly investigated as a therapeutic tool to treat chronic pain [4]. This principle has been previously used to treat orofacial pain, stimulating the motor cortex, with good results [5].

Anodic tDCS increases the excitability of the underlying cortex while cathodic tDCS decreases it; similarly, high-frequency repetitive transcranial magnetic stimulation (rTMS) increases cortical excitability, and low-frequency stimulation inhibits it. To a certain extent, both techniques have been shown to have similar effects when applied to treat chronic pain [6]. In BMS, an rTMS protocol using high-frequency stimulation applied to the left dorsolateral prefrontal cortex (DLPFC) has been used and proved to be effective in a randomized clinical trial [7].

Cognitive rehabilitation and therapeutic exercise have also proved to be effective for pain management [8] as sustained attention and executive functions are affected by chronic pain [9,10].

The main objective of this case report study was to test the efficacy of a multidimensional protocol based on transcranial Direct Current Stimulation (tDCS), cognitive–attentional therapy and therapeutic exercise for the treatment of psychophysical pain processing features in BMS patients. A secondary objective was to test if the effects are correlated with psychophysical pain processing changes or cognitive effects.

2. Materials and Methods

We present a case report study following the CARE checklist.

2.1. Case Presentation

A 74-year-old female with a 2 year history of a painful sensation on the gums and the palate is the subject of this work. The pain did not increase with palpation or movement but did in the case of emotionally stressful situations and hypervigilance to pain. Local and systemic causes were ruled out. Treatment with NSAIDs and opioids, topical clonazepam, alpha-lipoic acid, botulinum toxin and neuroleptics during the previous 18 months had not been successful.

2.2. Protocol

Outcome measures were assessed pre-intervention (day 1, measurement A) by two trained physical therapists and one neuropsychologist. In the following 2 weeks, the patient underwent 10 sessions of treatment (Monday to Friday). A final outcome measurement was performed twice, at the end of intervention (day 15, measurement B) and follow up (day 45, measurement C) after the end of the treatment sessions. The Verbal Numeric Pain Rating Scale (VNPRS) was administered every day from the first to the last measurement session, including the treatment sessions and the days of follow-up.

2.3. Outcome Measures

Psychophysical pain processing features were evaluated as primary outcome measures. Widespread mechanical hyperalgesia was calculated by adding up the mean of three Pain Pressure Thresholds (PPTs) (with 30 s rest between them) [11], assessed with a handheld pressure algometer (FPX Model, Wagner Instruments, Greenwich, CT, USA) at distant areas spread throughout the body: the right upper trapezius, the right epicondyle and the left anterior tibialis muscle. The PPT was applied with the algometer perpendicular to the skin, increasing at a rate of 1 kg/s [12] until the first sensation of pain. The reliability of algometry to assess PPTs has been shown to be good to excellent, with an intraclass correlation coefficient of 0.84–0.96 [13]. Temporal Summation (TS) was elicited through the application of 10 pulses of the handheld algometer with the intensity of the PPT,

previously calculated following the protocol above, over the middle of the distal phalanx of the left thumb [14]. In each pulse, pressure intensity increased at a rate of 2 kg/s over the previously determined PPT intensity, leaving an interstimulus interval of one second, according to the optimal method reported for inducing TS with pressure pain [15]. The patient was taught to rate the pain intensity of the 1st and 10th pressure pulses through the VNPRS, and the recorded punctuation was the result of subtracting the VNPRS score at the 10th pulse minus the VNPRS score at the 1st pulse. Finally, Conditioned Pain Modulation was evaluated after 5 min of finishing the TS task to prevent contamination. One PPT was assessed with algometry in the middle of the distal phalanx of the right thumb, corresponding to the first test stimulus. Afterwards, the immersion of the contrary hand up to the wrist into stirred ice-cold water (0–4 °C) for 3 min or until the pain was unbearable was used as the conditioning stimulus [16]. A second PPT was measured immediately after removing the hand from the cold water, corresponding to the second test stimulus. A third PPT was calculated 1 min later to assess the CPM residual functioning. The combination of PPT induced ba y handheld pressure algometer as a test stimulus and cold water as a conditioning stimulus is considered to be the most reliable method to assess CPM [17].

The secondary outcome measures included were clinical pain and craniofacial disability, assessed by the VNPRS, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale [18], by the Brief Pain Inventory (BPI) [19], and by the Craniofacial Pain and Disability Inventory (CF-PDI) [20]; quality of sleeping was evaluated by the Pittsburgh Sleep Quality Index (PSQI) [21]; and oral health was measured by the General Oral Health Assessment Index (GOHAI) [22] and by the Oral Health Impact Profile (OHIP-14) [23].

Secondarily, other psychological and cognitive variables were measured through the following tests: Trail Making Test (TMT) [24], Stroop [25], Montreal Cognitive Assessment (MoCA) [26], Digits-Symbols of the Wechsler Intelligence Scale III [27], State–Trait Anxiety Inventory (STAI) [28], Beck Depression Inventory II (BDI-2) [29], and Pain Catastrophizing Scale (PCS) [30].

2.4. Intervention

The patient received 10 sessions of a combined protocol of transcranial Direct Current Stimulation (tDCS), cognitive therapy, and therapeutic exercise.

2.4.1. tDCS

The Sooma tDCS^{TM} medical stimulator device was used. The left Dorsolateral Prefrontal Cortex was the chosen target as this was previously effective in an rTMS trial published by Umezaki et al. [7]. Active anodal tDCS was applied using surface sponge electrodes (35 cm^2). The cathode was placed over the contralateral supraorbital area, and a constant current of 2 mA was induced for 20 min [31].

2.4.2. Cognitive Therapy

During each stimulation session with tDCS, the patient underwent a 30 min session of cognitive training focused on improving sustained attention and executive functions, primarily inhibition through the cognitive rehabilitation platform NeuronUP (Neuronup SI, La Rioja, Spain).

2.4.3. Therapeutic Exercise

The patient was instructed to perform a jaw movement exercise protocol once a day over the course of the 10 sessions of treatment. The patient was instructed to move their jaw slowly and painlessly while watching herself in a small mirror [8].

2.5. Data Analysis

The effect size was calculated using the following formula: second score-first score/standard deviation. Effect size values above 0.80 were considered high and therefore to indicate a significant change.

3. Results

The results are shown in Table 1. The effect size is larger than 0.80 for the conditioned pain modulation between measurements A and B and B and C. The rest of the outcome measures had small effect sizes.

Table 1. Results and size of effect.

Data Sampling Time		A Day 1	B Day 15	C Day 45	A vs. B	A vs. C	B vs. C
					d	*d*	*d*
Objective pain measurements							
Widespread mechanical hyperalgesia	SD: 6.46	12.2	8.66	12.48	−0.54	0.04	0.59
Temporal summation	SD: 13.59	19	21	25	0.15	0.44	0.29
Conditioned pain modulation	SD: 1.31	2.36	−0.78	1.66	**−2.40** *	−0.53	**1.86** *
Pain, disability, quality of sleep and oral health							
PSQI	SD: 3.53	31	25	25	**−1.70** *	**−1.70** *	0
BPI	Intensity SD: 2.09	26	20	26	**−2.86** *	0	**2.79** *
	Functionality SD: 2.25	49	39	45	**−4.44** *	**−1.77** *	**2.66** *
PCS	SD: 6.92	34	25	15	**−1.3** *	**−2.73** *	**−1.44** *
LANSS	SD: 5.38	14	9	5	**−0.93** *	**−1.68** *	−0.75
IDCP-1/2	SD: 1.34	33	31	29	**−1.49** *	**−2.98** *	**−1.49** *
GOHAI	SD: 9.37	24	24	24	0	0	0
OHIP-14	SD: 3.03	39	38	39	−0.33	**−3.34** *	**−3.01** *
Cognitive measures							
TMT	A SD: 14.6	92″	77″	69″	**−1** *	**−1.53** *	−0.53
	B SD: 58,4	261″	160″	124″	**−1.40** *	**−1.89** *	−0.49
Stroop	Word SD: 18	68	83	86	**0.83** *	**1**	0.16
	Color SD: 14	28	33	37	0.35	0.64	0.28
	Word–color SD: 10	16	13	18	−0.3	0.2	0.5
MoCA	SD: 3.7	21	27	26	**1.62** *	**1.35** *	−0.27
WAIS III: Digit-Symbol	SD: 17.68	18	26	30	0.45	0.67	0.23
STAI	State. SD: 11.93	25	22	28	−0.25	0.25	0.5
	Trait. SD: 10.05	15	19	18	0.39	0.30	−0.10
BDI-2	SD: 10.9	29	25	30	−0.09	−0.46	−0.37

Note: SD: standard deviation. PSQI: Pittsburgh Sleep Quality Index; BPI: Brief Pain Inventory. IDCP-1/2: Inventory of Disability and Craniofacial Pain; GOHAI: General Oral Health Assessment Index; OHIP: Oral Health Impact Profile; PCS: Pain Catastrophizing Scale; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs; TMT: Trail Making Test; MoCA: Montreal Cognitive Assessment; WAIS III: Wechsler Intelligence Scale III; STAI: State–Trait Anxiety Inventory; BDI-2: Beck Depression Inventory II; A: day 1; B: day 15; C: day 45; *d* A vs. B: value of *d Cohen* between measurements A and B; *d* A vs. C: value of *d Cohen* between measurements A and C and *d* B vs. C: value of *d Cohen* between measurements B and C. * Large effect size.

3.1. Visual Numeric Pain Rating Scale

Regarding the VNPRS, a decrease in pain intensity of 47% (58/100 (pre), 11/100 (post)) was found. A follow-up was carried out for 45 days, in which the intensity of pain was recorded according to VNPRS. It was observed in the days following the intervention that the level of pain increased until reaching the level of the initial evaluation (increase in pain intensity of 50 points out of 100). The results are shown in Figure 1.

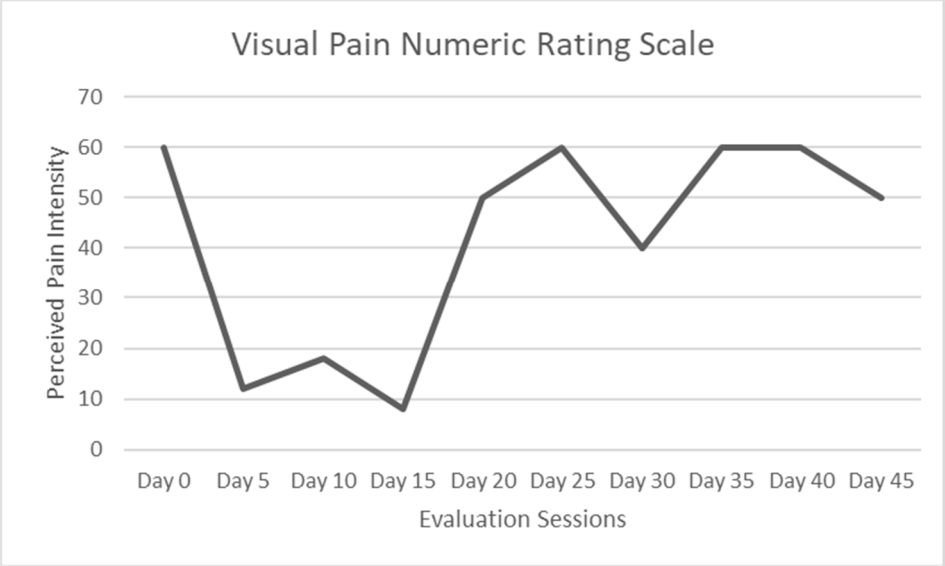

Figure 1. Results of the visual analogue scale during therapy and follow up.

3.2. Pain, Disability, Quality of Sleep and Oral Health

The results indicate a change in the LANSS scale between measures A and B and A and C. In the BPI scale differences were found in pain intensity between measures A and B and B and C. The effect size results indicate a change between measurements A and B and B and C in PSQI. In functionality, a large effect size was found in all measures, as in the IDCP-1/2 scale. On the OHIP-14 scale, we found a large effect size between measures A and C and B and C. The results are shown in Table 1.

3.3. Cognitive Measures

A high effect size was found in the TMT-A and TMT-B tasks when comparing measures A and B and A compared to C. There was only an evident change in the Stroop task in the condition of the word when comparing measures A and B and A compared to C, the same happens with MoCA. Finally, in the PCS scale, we found a high effect size among all measures.

4. Discussion

A multidimensional protocol based on transcranial Direct Current Stimulation (tDCS), cognitive–attentional therapy and therapeutic exercise was applied to a BMS-affected woman with a 45-day follow-up.

TDCS was used previously in other cranial pain conditions with good results [32]. The most common target for stimulation in pain has been M1, but DLPFC has also shown good effects in chronic pain conditions [33]. As Umezaki et al. [7] showed the effectiveness of DLPFC stimulation specifically in BMS, we chose this target for our protocol. In our case, there was an improvement in the subjective perception of pain with changes in VNPRS scores, but the effect disappeared at 45 days during the follow-up period (Figure 1). Large effect sizes were found in pain questionnaires (BPI, PCS and LANSS) and disability (IDDC, OHIP), and all except LANSS continued to improve after the end of the intervention. All of the changes persisted at 45 days of follow-up.

These results are in line with those of Umezaki et al. [7], who applied 10 sessions of rTMS on DLPFC and found an improvement in pain intensity immediately; as in our study, they found a worsening at one month of follow-up, but in their study, an improvement was seen 2 months later. We could not prove this further improvement as our follow-up period was limited to 45 days. According to Umezaki et al., these results suggest that the analgesic and antidepressant effects of non-invasive transcranial stimulation may act independently and suggest that inhibitory activation as a consequence of DLPFC stimulation by rTMS, used in their study, could be due to an improvement of limbic system dysfunction in patients with BMS. Although tDCS on the left Dorsolateral Prefrontal Cortex has been shown to be effective in improving affective symptoms [34], there were no changes in the anxiety and depression scales in our case, which may mean that there are effects beyond emotional improvement justifying the effects of this protocol.

Although the action mechanisms of tDCS are not yet fully understood, it has been suggested that the modulation of cortical excitability induces an activation of descending inhibitory pain systems [35]; surprisingly, in our case, there were no changes in objective pain measurements (widespread mechanical hyperalgesia and temporal summation) at any point. Contrarily to what was expected, Conditioned Pain Modulation significantly worsened when measured immediately after finishing the 10 sessions of the treatment protocol, returning to the baseline at day 45. These changes may be justified by the studies by Giordano et al. [36], which found that the daily application of tDCS may produce a neuroinflammatory effect that conditions the results of objective pain measurements just after completing the protocol. The transient worsening of CPM may be seen also seen as part of the nocebo effect that may have been caused by the end of the protocol [37]. CPM has been shown to decrease with aging [38]. Considering that CPM possibly predicts exercise-induced analgesia [39], therapeutic exercise may not have been a crucial factor on the effects of our protocol.

On the other hand, the cognitive effects of the protocol show an improvement in processing speed and executive control as well as sustained attention (improvements on TMT A and B task and Stroop-word) that persisted at one month of follow-up. Due to the relationship between executive function and pain, the improvement in pain perception may be explained in part by the improvement in the tasks that mediate the executive function [40].

Unexpectedly, an improvement in the MoCA score was also observed, improving from mild cognitive impairment to performance within normal limits; this may be due to the attention improvement on the performance of certain tasks of the test as the TMT-B.

The optimal duration of treatment varies depending on the published protocols, and while 10 sessions is the most common approach, further studies are needed to reach a consensus about the optimal number of sessions for orofacial pain treatment.

Regarding jaw exercises, a meta-analysis suggests moderate to significant effects from the combination of non-invasive brain stimulation and exercise in chronic pain, although the potential theoretical framework for this synergistic effect is controversial [41].

Our study, as with any case report, is limited by the individual pain characteristics and background that may condition the response to interventions and the lack of intervention control. Moreover, a possible limitation of this study may be the lack of other quantitative sensory tests, such as cold and heat detection thresholds, cold or heat pain thresholds or pinprick tests for TS. Nevertheless, our evaluation of the psychophysical results supports the hypothesis that chronic pain conditions maladaptive neuroplasticity, producing an imbalance in the allocation of attentional and cognitive resources and resulting in a misperception of pain [42]. Thus, behavioral therapies combined with non-invasive neuromodulation and therapeutical exercise may be effective in reducing pain perception and should be further encouraged [43].

5. Conclusions

This case report suggests that multimodal treatment based on tDCS, cognitive rehabilitation and therapeutic exercise may have positive effects on pain perception, disability,

pain catastrophizing and oral health. The improvement was independent of changes in psychophysical pain processing but correlated with improvements in processing speed, executive control and sustained attention. BMS remains a challenging medical condition to treat, and further research into the creation of treatment protocols using combined therapies is required. Our findings underline the importance of cognitive rehabilitation for pain management. Efficacy measurements of pain treatment protocols should consider cognitive evaluation. Psychophysical pain processing measurements should be interpreted cautiously considering that they may not always be correlated with clinical improvement.

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Informed Consent Statement: The patient was informed of the details of the evaluation and gave their written consent to participate in this study and to publish this paper, in accordance with the Declaration of Helsinki.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding authors (J.P.R.; J.F.-C.) upon reasonable request.

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