

Noninvasive transcranial direct current stimulation (tDCS) for the treatment of orofacial pain

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Abstract

OBJECTIVE: tDCS is a promising method for the treatment of chronic pain. Electrode placement locations must be chosen in accordance with the density and the time course of the current in order to prevent pathological changes in the underlying tissue. In order to reduce current spatial variability, more electrodes of the same polarity are placed in a circle around the second electrode of the opposite polarity. The applied current produced the greatest changes directly beneath the electrodes: the cathode reduces the excitability of cortical neurons, while the anode has the opposite effect.

METHODS: Based on inclusion criteria, 10 patients with chronic orofacial pain, secondary trigeminal neuralgia after oral surgery, were enrolled and underwent both anode and cathode stimulation. Before the first session we measured pain intensity on a numeric pain rating scale and tactile and thermal stimulation were used to assess somatosensory status. tDCS was applied for five consecutive days. At the end of tDCS application, somatosensory status was assessed again.

RESULTS: From our results we can conclude that the application of tDCS improves the perception of some types of pain. When we increase our sample size, we would expect confirmation not only on our positive results, but also some additional findings for explaining the pathophysiology of orofacial pain. These pathophysiological findings and explanations are very important for the application of tDCS in the treatment of orofacial pain and also for other types of neuropathic pain.

INTRODUCTION

Transcranial direct current stimulation (tDCS) is a simple, non-invasive neurostimulation technique which uses cathode / anode stimulation. It is applied on the head using low intensity direct current (0.029 to 0.08 mA/cm²) to stimulate the surface of the skull. We used this method for chronic orofacial pain that was refractory to pharmacotherapy. Although tDCS studies promise to

modulate cortical regions associated with pain, the electric current produced usually spreads beyond the area of electrode placement (Da Silva 2015).

Orofacial pain

Data from the European Union (2010) shows that the prevalence of chronic pain to be 19% of the European Union population (501,06,4212). In

January 2010, this represented 80 million Europeans, who at the time of the survey suffered from moderate to severe chronic nonmalignant pain (EU 2010).

The prevalence of chronic pain in Denmark is estimated at 16% for moderate to severe nonmalignant pain and 20.2% for chronic pain, in general. The prevalence of moderate to severe nonmalignant pain in Sweden is similar (18%). This is also comparable with the Netherlands and Germany (18% and 17%, respectively). In Italy the prevalence of nonmalignant pain appears to be higher (26%) (Reid *et al.* 2011).

In the United States, the prevalence of chronic pain was reported to be 30.7% of the population. With the incidence of pain in females (34.3%) being higher than in men (26.7%); and in agreement with the research, the prevalence seems to increase with age. The most commonly reported chronic pain were low back pain (8.1%) and primary osteoarthritis (3.9%). Half of those with chronic pain reported daily pain with the average intensity level, over the last 3 months, being ≥ 7 on the NPRS-Numeric Pain Rating Scale, which ranges from 0–10. American authors also reported that chronic pain occurs in about 30% of the adult population, although some authors have reported lower numbers (around 10%), while others set the prevalence at around 50%, although, mainly in developed countries (Johannes *et al.* 2010). Data from the Czech Republic regarding the prevalence of chronic pain are not available.

The social problem is not only in chronic pain as a single disease, but particularly pain which is refractory to conventional analgesics, i.e., chronic intractable pain.

The most common cause of orofacial pain is pain of dental origin that follows dental treatment or dental surgeries. Pain can cause by untreated tooth decay, inflammation of the dental pulp (pulpitis), or periodontal inflammation (periodontitis). Inflammation is usually restricted to the root area or affects the whole periodontal socket. A collection of pus in the periodontal crevice formed by a periodontal abscess or inflammation can spread to the surrounding bone tissue as alveolitis, osteitis, or osteomyelitis. Inflammation can get into the tissue in three ways: (1) bone injury, (2) complications such as periodontitis, or (3) the hematogenous pathway in primary osteomyelitis. Thorough intraoral examinations, testing of thermal sensations (heat and cold) and an X-ray examination are all important. Pain, especially in the acute stage radiates from the upper jaw to the temporal area and/or into the ear (sometimes simultaneously) and from the lower jaw to the neck. Prevention, through early dental care is the best way to avoid these types of pain. Chronic pain arising after dental procedures or surgeries is not uncommon and are often intractable (Fricová *et al.* 2013)

Neurostimulation methods

Neurostimulation methods, in the treatment of pain, are most useful and beneficial to patients suffering from intractable chronic pain and are used mainly

in chronic pain that was unresponsive to other long-term treatments (Simpson, 2003). Neurostimulation methods are indicated for patients with chronic neuropathic pain that lasts longer than six months and is usually refractory to well-established analgesic therapy (i.e., refractory to first and second-line treatment and/or accompanied by unacceptable side effects) (Nizard *et al.* 2012).

Neuromodulation methods provide a non-destructive and reversible approach to treating very strong, otherwise uncontrollable chronic orofacial pain, which is characteristically pharmacoresistant. Therefore, this method has a curative character. Reconstructive neurosurgery nowadays is based on the fact that instead of surgical destruction of neural pathways or nuclei began to stimulate neural structures. Neural stimulation is very effective in pain treatment; however, thalamic stimulation did not produce the expected results. These studies, however, may have been unnecessary, because as it turns out deep brain stimulation for the treatment of Parkinson's disease is much more effective. Coincidentally, it was discovered that pain can be treated using spinal stimulation (stimulation of the posterior fascicles) and stimulation of specific regions of the motor cortex.(Guleyupoglu *et al.* 2013)

Repetitive transcranial magnetic stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) is a neuromodulation method using an electromagnetic coil placed over the patient's head to induce electrical current impulses within the brain tissue, thereby modulating brain activity. One of the limitations of the current technology is that rTMS does not affect the deeper structures of the brain, but it is known that rTMS can significantly influence the perception of pain (Medeiros *et al.* 2012). rTMS is one of the newer, more promising methods of neuromodulation for pain treatment. It provides painless and noninvasive stimulation of the cortex using a magnetic field. According to recent studies, this method is able to induce changes in the central nervous system at the cellular level, which include ionic and metabolic changes (Gentner *et al.* 2008). rTMS has been confirmed in the literature of psychiatric disorders as effective in the treatment of depression, acute mania, bipolar disorder, panic attacks, hallucinations, obsessive states, schizophrenia, catatonia, and post-traumatic stress disorder.(George *et al.*, 2007) Neurological stimulation has also been used effectively in Parkinson's disease, dystonia, in patients with tics, stuttering, tinnitus, seizures or epilepsy, or functional disorders of aphasia after a stroke. (Fricová *et al.* 2013) In October 2008 the rTMS method was approved by the United States FDA (Food and Drug Administration) for the treatment of unipolar depression, which is refractory to pharmacological treatment.

Neuromodulation methods, including rTMS represent significant progress in the treatment of chronic pain. rTMS is a very gentle, non-invasive method with

demonstrated success in the treatment of pain, which is a major step and represents a further shift toward non-invasive methods of pain therapy. rTMS, however, is not commonly used in the treatment of certain psychiatric and neurological disorders, but is used as a test for the application of electrical stimulation of the brain's motor cortex (Hasan *et al.* 2013) As a result of this testing, it was shown that in some cases, rTMS stimulation was prolonged the therapeutic effect offering a reduction and in some cases, complete elimination of chronic pain (Fricová *et al.* 2013). We decided to check on the patient cohort effect of this method mainly because we have our own experience with motor cortex stimulation (MCS). (Fricová *et al.* 2013). Our research team began using rTMS in the treatment of chronic orofacial pain 5 years ago, and has been used on 70 patients (Fricová *et al.* 2009). More recent studies suggest the involvement of the peripheral and central nervous system as a possible pathophysiology mechanism in atypical odontalgia (Fricová *et al.* 2013).

In addition, it can be assumed that rTMS and the necessary equipment will gradually make the technique universally accessible. The primary goal of our project was to demonstrate the curative effect of rTMS and tDCS on intractable chronic orofacial pain.

Transcranial direct current stimulation (tDCS)

Other non-invasive and simple neurostimulation techniques include tDCS, which uses a cathode and an anode that are placed to the head and through which a low current (from 0.029–0.08 mA/cm²) directly stimulates the surface of the skull. tDCS is a noninvasive stimulation technique that is affordable and easy to use compared to other neuromodulator techniques (Medeiros *et al.* 2012). Anode stimulation increases cortical excitability, while cathode stimulation decreases it. tDCS is a promising method for the treatment of chronic pain, as well as for patients with neuropsychiatric diseases and other neurological disorders (Guleyupoglu *et al.* 2013) Most of the current passes through the surface layer of the skin and only a small amount penetrates to the cortex. Electrode placement locations must be chosen in accordance with the density and the time course of the current in order to prevent pathological changes in the underlying tissue. In order to reduce current spatial variability, more electrodes of the same polarity are placed in a circle around the second electrode of the opposite polarity. The applied current produced the greatest changes directly beneath the electrodes: the cathode reduces the excitability of cortical neurons, while the anode has the opposite effect. The effect of stimulation can change be changed by changing the electrode surface area and current density. The effect of stimulation usually lasts several hours. tDCS is thought to be a promising method for treating chronic pain (O'Connel *et al.* 2014), as well as for patients with neuropsychiatric diseases and other neurological disorders (Kuo *et al.* 2014).



Fig. 1. Application of tDCS..

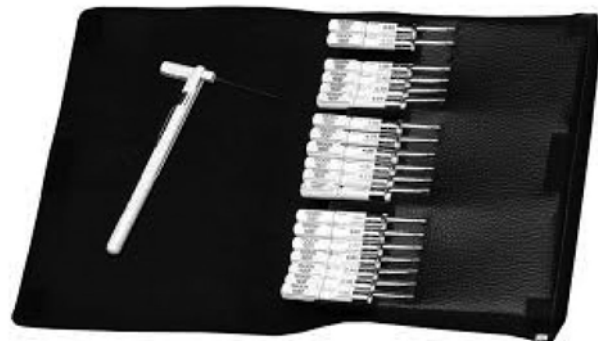


Fig. 2. Semmes-Weinstein monofilament to evaluate tactile sensation

MATERIAL AND METHODS

Before entering the study, patients are informed in details about its structure, the clinical course, and the effect of treatment. As part of the informed consent it was necessary to be familiar with the side effects and potential complications of therapy. Participation in the study was voluntary and without financial reward. Study inclusion criteria were as follows: a) syndrome of intractable orofacial pain diagnosed by a specialist, b) stable analgesic medication for at least 1 week before the study and throughout its course, c) 18–65 years of age, d) absence of severe organic brain damage or other serious diseases that could interfere with rTMS (e.g. epilepsy), and e) an available MRI (not older than two years). Based on these criteria, 10 patients with chronic orofacial pain, i.e., secondary trigeminal neuralgia after oral surgery, were enrolled and underwent both anode and cathode stimulation. Before the first session we measured pain intensity on a numeric pain rating scale and tactile and thermal stimulation were used to assess

somatosensory status. tDCS was applied for five consecutive days. At the end of tDCS application, somatosensory status was assessed again.

Before starting tDCS stimulation patients were assessed using a variety of questionnaires (e.g. M-Gill University, Beck Inventory, SF 36 quality of life, etc.). We felt that it was very important to know the subjective pain descriptions and subjective feelings of patients with regard to the impact of the chronic pain on their daily lives.

The HDC stim apparatus (Newronica) was used for tDCS. The patients were divided in two groups. Group 1 underwent actual tDCS, while Group 2 underwent sham stimulation. After each session the type of stimulation was changed, which means that ultimately all patients received both real and sham stimulation sessions.

The length, amplitude, the interval between two stimulations.

In each session used the following parameters: 1 mA, 20 minutes of stimulation. The cathode and anode were placed in the temporal side of skull and represented the projection of the dorsolateral prefrontal (DLPF) cortex.

Patient characteristics

The participants suffered from orofacial pain for average time of 6,125, average age of patients was 55,625 from 39 -71years. The location of the orofacial pain was: facial unilateral (5), chin (1), glossodynia (1), secondary neuralgia of trigeminus (1). As concern of the treatment in three cases it was no previous pain treatment. The rest of patients (7) used, antiepileptic drugs, antidepressant, and non-opioid analgesics. The complications from previous treatment were: sedation and dizziness.

RESULTS

Stimulation was assessed with respect to possible effects on clinical variables such as the origin of the pain (neuropathic, nociceptive), its localization, sensory deficit, and duration. Results were evaluated using the paired t-test. The Wilcoxon test was used when the data lacked a normal distribution.

NRS (Numeric rating pain scale)

Using the NRS, 62.5% of patients reported that tDCS reduced pain perception by $53.7\% \pm 31.5\%$, 12.5% reported that the pain was unchanged and 25% reported that the pain worsened by $53.3\% \pm 3.33\%$.

M-Gill questionnaire

The most common type of pain was described as a burning pain, which improved in 12.5% of cases and in 62.5% remained at the same level. Other commonly described pain was dull pain, sensitive to touch and tiring. The greatest improvement in pain occurred in

touch sensitive (42.9%), throbbing (40%), and irksome (40%) pain. No improvement was observed in pains described as sharp, stabbing, and gnawing like crack. The perception of pain worsened for pain described as crack (50%), stabbing (33.3%), spasmodic (33.3%), nagging (33.3%), and blunt (28.6%). The changes that occurred with the treatment were not great enough to exclude the possibility that the difference was due to chance ($t = 0.344$ (7 degrees of freedom), $P = 0.741$).

QST Quantitative thermal and tactile sensation

Thermal sensation affected vs. unaffected side before treatment: $t = 1.735$ (6 degrees of freedom), $P = 0.133$; no statistically significant difference. Thermal sensation affected vs. unaffected side after treatment: $t = 1.870$ (5 degrees of freedom), $P = 0.120$; no statistically significant difference.

Tactile sensation affected vs. unaffected side prior to treatment Wilcoxon test, $P = 0.37$; no statistically significant difference. Tactile sensation affected vs. unaffected side after treatment: $t =$ Wilcoxon test, $P = 0.37$; no statistically significant difference.

Beck depression inventory

A statistically significant difference was not observed (3 patients showed a slight improvement); $t = 0.509$ (7 degrees of freedom), $P = 0.626$.

Beck anxiety inventory

Beck Anxiety Inventory: $t = -0.429$ (7 degrees of freedom), $P = 0.681$; no statistically significant difference (4 patients reported improvement).

Pain detect

The change that occurred with the treatment is not great enough to exclude the possibility that the difference is due to chance ($t = 2.294$, (6 degrees of freedom), $P = 0.062$). The results obtained from these descriptions are only statistically significant results from this our pilot study.

DISCUSSION

A decrease in orofacial pain was seen especially after cathode stimulation. Based on our results we believed that cathode stimulation reduces excitability of cortical brain cells via hyperpolarization of the glutamate system. Cathode stimulation produces a homeostatic effect. (Fitzgibbon *et al.* 2016)

Our article represents a pilot study, since any definitive conclusion would require a much larger sample size. In our study we used objective psychological tests and we also assessed the subjective feelings of the patients in our sample

Da Silva (2015) compared the neuroanatomic location and strength of predicted electric current peaks at cortical and subcortical levels, induced by conventional and High-Definition-tDCS (HD-tDCS) in migraine and other chronic pain disorders. The electrodes were

positioned in accordance with the 10-20 or 10-10 electroencephalogram (EEG) landmarks: motor cortex-supraorbital, dorsolateral prefrontal cortex-bilateral, and vertex-occipital cortex. Peaks of current flow also occurred in deeper brain structures, such as the cingulate cortex, insula, thalamus, and brainstem. The same structures received a significant amount of current with Cz-Oz and DLPFC tDCS. However, there were differences in the current flow to outer cortical regions. The visual cortex, cingulate, and thalamus received the majority of the current flow with Cz-Oz, while the anterior parts of the superior and middle frontal gyri displayed an intense amount of current with DLPFC montage. HD-tDCS montages enhanced the focality, producing peaks of current in subcortical areas at negligible levels. This study provides novel information regarding the neuroanatomical distribution and strength of the electric current using several tDCS montages applied for migraine and pain control. Such information may help clinicians and researchers in deciding the most appropriate tDCS montage to treat each pain disorder (Da Silva 2015).

CONCLUSIONS

tDCS is a promising method of treatment for chronic pain. In a future project we would like to study the effect of tDCS on glial cells and its effect on neuroplasticity and neuroprotection. We would also like to evaluate the effect of tDCS on phantom pain, back pain, and eventually fibromyalgia.

From our results we can conclude that the application of tDCS improves the perception of some types of pain. When we increase our sample size, we expect confirmation not only the confirmations of our positive results, but also some finding for explaining the pathophysiology of orofacial pain. These pathophysiological findings and explanations are very important for the application of tDCS in the treatment of orofacial pain and also for the other types of neuropathic pain.

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