Journal of the Neurological Sciences 354 (2015) 103–109

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Prophylactic treatment in menstrual migraine: A proof-of-concept study

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ARTICLE INFO

Article history:
Received 18 December 2014
Received in revised form 4 May 2015
Accepted 6 May 2015
Available online 14 May 2015

Keywords:
Cathodal
Migraine
Prophylaxis
tDCS
Visual cortex
Repetitive transcranial stimulation

ABSTRACT

The present study aimed to investigate the efficacy of repetitive cathodal direct current stimulation (rctDCS) over the visual cortex as a prophylactic treatment in patients with menstrual migraine. 20 female patients were recruited in this double-blind, placebo-controlled study and were assigned to receive either cathodal or sham stimulation. Over 3 menstrual cycles, tDCS with 2 mA intensity and 20 min duration was applied to the visual cortex of the patients, in 5 consecutive sessions 1–5 days prior to the first day of their menstruation. The primary endpoint of the study was the frequency of the migraine attacks at the end of the treatment period, however, additional parameters, such as the number of migraine related days and the intensity of pain were also recorded 3 months before, during and 3 months post-treatment. Visual cortex excitability was determined by measuring the phosphene thresholds (PTs) using single pulse transcranial magnetic stimulation (TMS) over the visual cortex.

Sixteen patients completed the study. A significant decrease in the number of migraine attacks ($p = 0.04$) was found in the cathodal group compared to baseline but not compared to sham ($p = 0.053$). In parallel the PTs increased significantly in this group, compared to the sham group ($p < 0.05$).

Our results indicate that prophylactic treatment with rctDCS over the visual cortex might be able to decrease the number of attacks in patients with menstrual migraine, probably by modifying cortical excitability.

1. Introduction

For migraine, prophylactic therapy is often recommended to patients suffering from a strong intense and/or a high frequency of attacks. Although a broad range of pharmaceutical options exists, there is an increasing interest toward non-pharmaceutical alternatives with reduced side-effects to common prophylactic medications (e.g. [21,50,54]).

Several studies have demonstrated the efficacy of transcranial magnetic (TMS) and direct current stimulation (tDCS) in the acute and prophylactic treatment of migraine [5,18,20,34,35,37,43,53,55]. The effect of these stimulation methods is based on influencing neuronal activity and therefore, presumably, they can also interfere with the occurrence of cortical spreading depression [33]. Studies have shown that migraine headache was diminished or stopped by application of two-pulses of TMS over the visual cortex or over the painful area [18,34].

Concerning tDCS there is evidence at the cellular level that anodal tDCS and cathodal tDCS affect the different neuronal compartments [45,46]. It was suggested that anodal tDCS hyperpolarizes the membrane potential in the apical dendritic regions and depolarizes it in the somatic region, whereas the cathodal stimulation has a reversed effect. The estimation of the stimulation's effect on cortical excitability in humans is mostly performed by measuring the amplitude of the motor-evoked-potentials (MEPs) induced by single-pulse TMS [42] and might not be transferred to other stimulation montages over non-motor cortical areas.

With regard to the prophylactic application of tDCS in migraine, Antal [5] and coworkers treated patients with episodic and chronic migraine using cathodal versus sham stimulation over the visual cortex. In the active treatment group a significant reduction in the duration of the attacks, the intensity of pain and the number of migraine-related days post-treatment was observed compared to the baseline period, whereas the frequency of the attacks remained constant. However, compared to the sham group, only the intensity of the pain was significantly less, in case of a migraine attack. Vigano et al. [55] also reported a preventive effect of a two-weekly session of tDCS in migraine, however using excitatory anodal stimulation over the visual cortex. Dasilva and colleagues found comparable results by applying anodal tDCS, in this instance, over the primary motor cortex (M1) [20].

Taken as a whole, the results of previous papers exploring the efficacy of transcranial stimulation in migraine treatment are somewhat contradictory. This is partly due to methodological factors, such as using diverse stimulation protocols on heterogeneous patient populations. The present study aimed to investigate the efficacy of tDCS in a uniform subtype group of patients with menstrual migraine. It is estimated that approximately 50% of women with migraine have an increased risk of

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http://dx.doi.org/10.1016/j.jns.2015.05.009
0022-510X/

experiencing migraine during the premenstrual phase [37]. Menstrual migraine includes menstrual-related migraine, which is defined as migraine attacks occurring on days −2 + 3 of menstruation in at least two out of three cycles as well as at other times during the cycle, and pure menstrual migraine, in which migraine occurs only in association with menstruation on or between days −2 + 3 [1,26,49]. The most plausible trigger for menstrual migraine is the decline in serum estradiol levels. Declines in magnesium levels in the serum or sensitization of nociceptors by prostaglandins, released from the endometrium may also contribute to the development of pain. Furthermore, the decrease in the activity of the inhibitory neurotransmitter systems might result in increased firing of the neurons and increased neuronal excitability. Acute and short or long term preventative therapies may be used for the treatment. However, menstrual migraine has been reported to be more disabling and less responsive to acute therapy than non-menstrual migraine [1]. Short term prophylactic therapies are applied for 4–8 days and include non-steroidal anti-inflammatory drugs, triptans and estrogen transdermal patches/gel. Continuous prophylactic therapies include hormonal treatments or beta-blockers, calcium channel blocker, tricyclic antidepressants and anticonvulsants, usually with lots of side effects [37].

While in these patients the appearance of the migraine attack is highly predictable, we hypothesized that repetitive applications of cathodal tDCS (rctDCS) that are expected to have an inhibitory effect [4,6], applied over the visual cortex as a prophylactic treatment before the onset of menstruation, would decrease the likelihood of the occurrence of the next migraine attack.

2. Methods

2.1. Patients

Twenty female patients with menstrual migraine were recruited into the study. Inclusion criteria were: that the diagnosis must meet the 2004 IHS criteria ([26], specific criteria for menstrual migraine are in the appendix A) for migraine without aura or migraine with aura; the duration of the disease must be at least 6 months. Patients with chronic health disorders, diagnosed neuropsychiatric disorders, pregnant or breast feeding, with a history of substance abuse or dependence, and with a history of neurological disorders other than migraine were excluded. Patients who had an implanted pacemaker or metallic hardware in the head or scalp (e.g. surgical clips) were not included in the study. Patients were advised to maintain the pain medication (in case of an attack) and contraception (that was started a minimum of 6 months before the enrollment into the study) during the whole study period. None of the patients were acute migraine medication abuser. During the study four patients, two from the sham and two from the active groups, dropped out (see Fig. 1. and Results section below). Sixteen patients completed the study (Table 1).

All aspects conformed to the Declaration of Helsinki; written informed consents were given by all study participants. The experimental protocol was approved by the ethics committee of the Medical Faculty of the University of Göttingen.

2.2. Experimental design

This study was a double-blind, placebo-controlled study. The primary endpoint of the study was the frequency of the migraine attacks, the secondary efficacy endpoint the number of migraine-related days (the number of days on which the patients had migraine-related symptoms). The study had three phases (Fig. 1.): (i) baseline period, consisting of 12-weeks in which the frequency of the migraine attacks was recorded, including the onset and duration of the pain and the number of migraine-related days and the type of analgesics taken in case of a migraine attack; (ii) a 12-week treatment period, consisting of 3 × 5 treatment sessions with either sham or cathodal tDCS (20 min) for 5 days before the expected onset of the menstruation; and (iii) a follow-up period of 12-weeks to further record the abovementioned parameters. Patients were asked to maintain a headache diary throughout the duration of the entire study period.

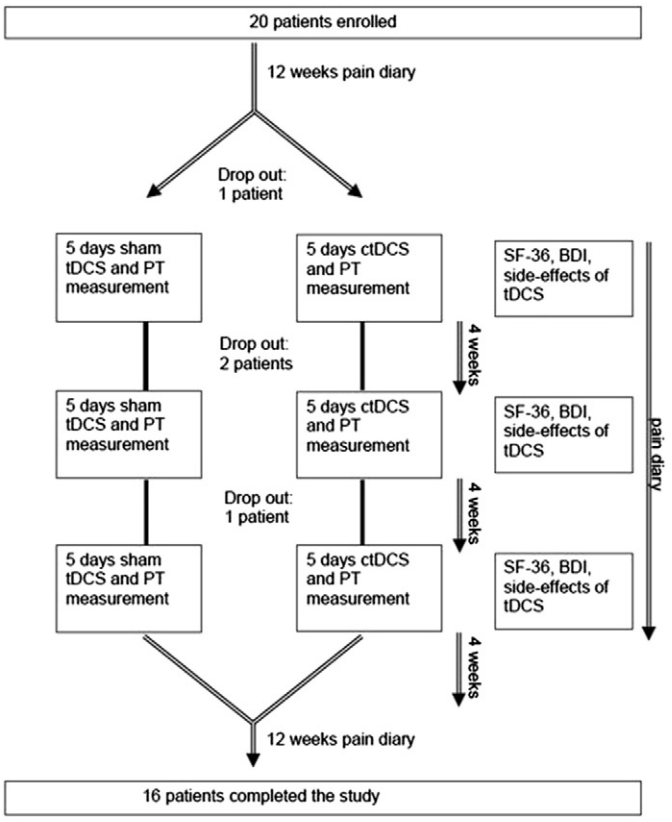

Fig. 1. Graphical sketch of the 9 month study period. The study included three phases, each consisting of 12 weeks. During the first period the frequency and the duration of the migraine attacks were documented. The subsequent phase consisted of the repeated application of a five-day cathodal or sham treatment. In a follow-up period the frequency and the duration of the migraine attacks were recorded. PT: phosphene threshold.

Table 1
The demographical characteristics and medical history of the patient group indicated using means and SDs.

	Cathodal	Sham
With aura	2	2
Without aura	6	6
Mean age (SD)	31,6 (6,2)	27,1 (4,4)
Mean duration in years (SD)	12,1 (5,1)	9,8 (6,5)
Mean number of attacks/year (SD)	14,7 (4,5)	13,9 (2,5)
Side(s) of pain		
One	7	6
Both	1	2
+ Family history	8	7
Medication		
ASS (Aspirin®)	1	1
Triptans	2	3
Ibuprofen	7	4
Paracetamol	2	3
Others	1	1
Contraception		
Oral	5	5
NuvaRing	1	2
Nicotin	1	3