ARTICLE IN PRESS

Brain Stimulation xxx (2015) 1–10

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Transcranial Direct Current Stimulation in Epilepsy

Daniel San-juan [a,*], León Morales-Quezada [b], Adolfo Josué Orozco Garduño [a], Mario Alonso-Vanegas [c], Maricarmen Fernández [a], Dulce Anabel Espinoza López [a], Rafael Vázquez Gregorio [a], David J. Anschel [d], Felipe Fregni [b]

[a] Neurophysiology Department, National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez", Av. Insurgentes Sur 3877, Col. La Fama, Tlalpan, México D.F. 14269, Mexico
[b] Laboratory of Neuromodulation, Department of Physical Medicine & Rehabilitation, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, 300 1st Ave, Charlestown, MA 02129, USA
[c] Neurosurgery Department, National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez", Av. Insurgentes Sur 3877, Col. La Fama, Tlalpan, México D.F. 14269, Mexico
[d] Comprehensive Epilepsy Center of Long Island, St. Charles Hospital, 200 Belle Terre Rd., Port Jefferson, NY 11777, USA

ARTICLE INFO

Article history:
Received 4 July 2014
Received in revised form
2 January 2015
Accepted 5 January 2015
Available online xxx

Keywords:
Transcranial direct current stimulation
tDCS
Brain polarization
Galvanic stimulation
Epilepsy

ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is an emerging non-invasive neuromodulation therapy in epilepsy with conflicting results in terms of efficacy and safety.
Objective: Review the literature about the efficacy and safety of tDCS in epilepsy in humans and animals.
Methods: We searched studies in PubMed, MedLine, Scopus, Web of Science and Google Scholar (January 1969 to October 2013) using the keywords 'transcranial direct current stimulation' or 'tDCS' or 'brain polarization' or 'galvanic stimulation' and 'epilepsy' in animals and humans. Original articles that reported tDCS safety and efficacy in epileptic animals or humans were included. Four review authors independently selected the studies, extracted data and assessed the methodological quality of the studies using the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions, PRISMA guidelines and Jadad Scale. A meta-analysis was not possible due to methodological, clinical and statistical heterogeneity of included studies.
Results: We analyzed 9 articles with different methodologies (3 animals/6 humans) with a total of 174 stimulated individuals; 109 animals and 65 humans. *In vivo* and *in vitro* animal studies showed that direct current stimulation can successfully induce suppression of epileptiform activity without neurological injury and 4/6 (67%) clinical studies showed an effective decrease in epileptic seizures and 5/6 (83%) reduction of inter-ictal epileptiform activity. All patients tolerated tDCS well.
Conclusions: tDCS trials have demonstrated preliminary safety and efficacy in animals and patients with epilepsy. Further larger studies are needed to define the best stimulation protocols and long-term follow-up.

Introduction

Transcranial direct current stimulation (tDCS), a non-invasive method that modulates cortical excitability, has reemerged as a technique of active investigation. Systematic research on tDCS dates back to the 1960s, but despite some reports the technique has not gained general clinical acceptance [1]. Initial therapeutic applications of tDCS focused on neuro-behavioral disorders. Many of these studies have been merely exploratory and the positive results have yet to be reproduced. Pathologies on which studies have been conducted include; Parkinson's disease [2], cerebrovascular events [3], central pain [4,5], fibromyalgia [6], major depression [7], Alzheimer's Disease [8] and, most recently, epilepsy [9–13].

Epilepsy treatment options based on neurostimulation such as chronic intermittent vagal nerve stimulation (VNS), cortical brain stimulation, deep brain stimulation and transcranial magnetic stimulation (TMS) have gained international attention in recent years [14–17]. The underlying principle of these techniques relies on the idea that extrinsic stimulation can reduce hyperexcitability or interfere with the discharges of epileptogenic networks [15]. VNS alone or in combination with antiepileptic drugs (AEDs) offers the possibility of improving quality of life by controlling seizures, minimizing the systemic load of AEDs and improving mood [18]. Despite the hopes and expectations that were raised by VNS, its efficacy has been limited and comparable to the introduction of a new AED [15,16]. VNS is also not exempt from complications and

* Corresponding author. Tel.: +52 5556063822x2527; fax: +52 5556064532.
E-mail address: pegaso31@yahoo.com (D. San-juan).

http://dx.doi.org/10.1016/j.brs.2015.01.001
1935-861X/

adverse cardiovascular, phonatory, respiratory and, gastrointestinal reactions during its implantation and subsequent use [14,17]. Deep brain and cortical stimulation techniques have gained some acceptance, including US FDA approval for two devices (Responsive Neurostimulation System (RNS), Neuropace, Mountain View CA and Deep Brain Stimulation (DBS), Medtronic, CA). However, optimal stimulation parameters as well as selection of best possible targets are not yet clearly defined. Furthermore, these devices require surgical implantation [19,20].

tDCS is applied through two electrodes (anode and cathode) over the skull to induce widespread changes of cortical excitability through a weak constant electric current. Cortical excitability may increase following anodal stimulation, while it generally decreases after cathodal stimulation [1,21]. Based on this principle, hyperpolarization using cathodal tDCS has been proposed as therapy to suppress epileptiform discharges and clinical seizures in basic and clinical studies.

Compared to VNS, DBS and RNS; tDCS and repetitive transcranial magnetic stimulation (rTMS) are non-invasive techniques [15,22]. However, tDCS has several advantages over rTMS in that it is more economical and it can be safely used with compact equipment [7]. The present review focuses on analyzing the information on the efficacy and safety of tDCS in epilepsy in humans and animals.

Material and methods

Our systematic review was conducted according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [23], and the present report follows PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [24].

Literature search

We searched for articles in PubMed, MedLine, Scopus, Web of Science and Google Scholar from January 1969 to October 2013 using the keywords 'transcranial direct current stimulation' or 'tDCS' or 'brain polarization' or 'galvanic stimulation' and 'epilepsy' in animals and humans. We also looked for articles in the reference lists of retrieved articles and tDCS review articles and contacted experts in the field.

Selection criteria

The following criteria were adopted: (1) articles written in English (although there were no manuscripts in other languages), (2) original articles and (3) case reports. We therefore excluded the following articles: (1) review articles; (2) articles reporting duplicate data or data extracted from original articles; (3) articles addressing only the effects of other brain stimulation techniques such as alternating electrical current stimulation or rTMS.

Data extraction

For each study, two authors extracted data independently (D.S and A.O.G.) and two other authors (L.M.Q. and F.F.) checked data extraction. Any discrepancies were resolved by consensus with the corresponding author (D.S.) consulted if necessary. We elaborated a structured checklist in order to extract the following variables: (1) Demographic and clinical characteristics, such as total sample, animals or humans, sex (male/female), type of epilepsy, model of epilepsy, and age (years). (2) Study design characteristics, such as frequency of stimulation sessions and control group. (3) Treatment characteristics, which included anode and cathode positioning, dose of electric current (mA), size of electrodes (cm^2), type of electrodes, duration of session (min), current density (A/cm^2), which was calculated using the formula:

$$J = I/a$$

where J = current density (A/m^2), a = contact surface area (m^2) and I = electric current (A), and electric charge (C) (calculated using the formula described in Brunoni AR et al., 2011 [25]):

$$Q = I/t$$

where Q = electric charge, I = electric current, and t = time (s).

(4) Adverse effects (AEs), in which we considered either an 'all-or-none' reporting (e.g. 'all patients tolerated treatment well'; 'all subjects reported a tingling sensation'; 'no side-effects were reported', etc.) or a detailed description of adverse events – in such cases, we collected data on reporting of itching, burning, tingling, discomfort, and headache. These adverse events were chosen because comprehensive reviews and a consensus article regarded them as common events related to the stimulation [26,27]. (5) In order to better understand we defined efficacy as the reduction of inter-ictal epileptiform activity or percentage reduction of clinical seizures.

Quality assessment

According to the methodology of Jadad [28] we addressed the following issues that influence data quality: (1) selective outcome reporting [29] – we identified whether and to what extent AEs and outcomes were reported; which method (passive monitoring vs. active surveillance) was used for assessing AEs or efficacy; and whether studies reporting AEs and efficacy discussed them or not; (2) year of publication [23] and (3) presence of control group.

Since our aim is to identify safety and efficacy related to tDCS, we took a broad approach and did not discard studies based on risk bias; instead, we undertook separate analyses according to study quality.

Quantitative analysis

All analyses were performed using Excel and due to the small number of studies, we showed the results using descriptive statistics. A meta-analysis was not possible due to methodological, clinical, and statistical heterogeneity of included studies.

Results

We retrieved 166 articles. However, after excluding studies according to our selection criteria, 9 articles with different type of design (3 animals/6 humans) were selected with 109 animals and 65 humans with epilepsy; 8 articles presented more than one experiment and no articles presented duplicated studies (Fig. 1). In total 5/65 (8%) epileptic patients – 4 tDCS and 1 sham group – reported mild AEs. All clinical studies presented a high risk of bias.

Basic research on tDCS in epilepsy

Table 1 summarizes the results of animal studies using tDCS. *In vivo* studies showed favorable results applying tDCS to treat induced epileptic seizures in rats. The first study, by Liebetanz et al. (2006), evaluated the antiepileptic potential of tDCS in a modified cortical ramp-stimulation seizure model in rats. To determine the threshold for localized seizure activity (TLS) in this model, a single train (50 Hz; 2 ms; 2 μA) of bipolar rectangular pulses with steadily increasing current intensity was applied through a unilateral epicranial electrode to the cortex. When the first signs of convulsive behavior were registered, stimulation was interrupted and the point defined as the TLS. In four sessions, one group ($n = 7$) received tDCS