Pakistan Journal of Neurological Sciences (PJNS)

Volume 13 | Issue 1 Article 11

3-2018

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Direct Current Stimulation and Epilepsy in Developing Countries: Opportunity and Challenges

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Date of submission: *September 23, 2017* ***Date of revision:*** *November 29, 2017* ***Date of acceptance:*** *December 13, 2017*

ABSTRACT:
Transcranial direct current stimulation (tDCS) is one type of neuromodulation, which is an emerging technology that holds promise for the future studies on therapeutic and diagnosis applications in treatment of neurological and psychiatric diseases. Epilepsy is one of the commonest neurological disorders, caused by an enhanced cortical excitability favoring paroxysmal neuronal discharge. Cathodaldirect current stimulation (ctDCS) is a low-cost non-invasive portable neuro-stimulatory technique which can transiently decrease cortical excitability in humans. This was invasively demonstrated to reduce epileptiform discharges in animals.

INTRODUCTION:

Epilepsy affects approximately 50 million people worldwide, and 80% of them live in the developing world [1, 2]. Epilepsy is a chronic disorder which not only affects the patient but also the entire family. An individual is diagnosed to have epilepsy if they have two or more unprovoked seizures occurring greater than 24 hours apart. Seizures are casued by abnormal electrical activity in the brain and can present in a variety of forms like tonic-clonic activity of one limb or entire body, staring, eye blinking, sudden jerks, sudden loss of tone leading to falls. They can also present as an abnormal sensation perceived by the patient. Patient can have preserved awareness, altered awareness or even loss of consciousness during a seizure. They are usually brief lasting one to two minutes but some seizures can be prolonged. If the seizure lasts more than five minutes, it is considered as status epilepticus.During some seizures patients can have bowel or bladder incontinence. Some individuals continue to have frequent seizures despite optimal treatment with anti-seizure drugs. However, more than 70 percent of patients who are treated achieve long-term remission or freedom from seizures, normally within 5 years of diagnosis [2].

Approximately 60% of patients with epilepsy have some form of focal epilepsy, and 35% of this cohort have an unsatisfactory response to anticonvulsant medications (AEDs) [3]. Surgical therapy for intractable neocortical epilepsy (NE) remains suboptimal and may produce neurologic deficits not predicted from pre-surgical evaluation—an especially serious problem in children [4, 5]. Although pre-surgical imaging and electrophysiologic localization of the epileptic focus continue to improve, up to 80% of resections for non–temporal lobe epilepsy yield less than excellent outcomes [6]. The relatively disappointing results with present surgical techniques have led clinical study epileptologists to explore other approaches to treating focal seizures, including external electrical fields, local cortical stimulation with implanted electrodes, and microinjection of AEDs [5-7].

Available pharmacological strategies for seizure relief in patients with neocortical epilepsy can be ineffective, and are associated with prominent side effects such as psychological and behavioral changes. Up to 35%of patients with neocortical epilepsy experience drug-resistance. Furthermore, precise localization of the seizure focus for surgical resection is often difficult. A particular challenge in the evaluation of intractable neocortical epilepsy patients is that in about 30% of extra-temporal epilepsy cases, brain MRI does not identify a lesion[8].Therefore, a non-pharmacologic, non-surgical method to treat neocortical epilepsy with limited side effects, either in the hospital or home setting, remains an unmet medical need.

Consequences of Epilepsy

A variety of treatment modalities are available in the form of drugs, Ketogenic diet, Vagus nerve stimulation (VNS), Responsiveneurostimulation (RNS) and epilepsy surgery. These modalities enable the majority of people with epilepsy (PWE) to control their seizures, but in about 30-40% seizures persist inspite of different treatment modalities [3]. In many countries, this disorder is still shrouded in secrecy and patients prefer not to reveal or discuss their condition [4]. Understanding the unique and complex impact of epilepsy on a person's quality of life (QOL) is also increasinglyrecognized as an important component of clinical care [5],

and research in this area will identify factors affecting quality of life QOL and may lead to strategies that improve the management of epilepsy.

Patients with epilepsy diagnosed in childhood could have many schooling hours disrupted, if the frequency of seizures were high and this could lead to low educational achievement and thus a lower employability potential. Occupational related stress with assignment deadlines and criticisms by supervisors can be stressful enough to trigger seizures [7]. Moreover, seizure itself sometime causes accidentsand injuries thus preventing sufferers from driving and depriving them from many types of employment opportunities. Employers usually do not give jobs to persons with epilepsy if they are experiencing seizures that interfere with job performance [8].

Nonetheless, a vast majority of individuals with epilepsy in many resource-poor regions do not receive treatment [9, 10]. Seizure remission is possible with appropriate use of anti-seizure drugs. Epileptic patients who were treated withanti-seizure drugs had significantly better QOL than the untreated people [10]. Monotherapy has been recognized to be able to control seizures adequately in about 50% of patients with epilepsy and polytherapy is only necessary in the minority of people with more severe seizures.

Untreated epilepsy is a critical public health issue, as people with untreated epilepsy face potentially devastating social consequences and poor health outcomes. Due to stigma, many persons with epilepsy have lower employment and education levels and lower socioeconomic status. For example, children with epilepsy who have a seizure at school may be rejected, while adults may be barred from marriage or employment [11-14]. Psychiatric diseases such as depression and mood disorders have been reported to be common among PWE and are important determinants of QOL [15,16].

People with uncontrolled epilepsy have a fear of next seizure and may take precautions and impose restrictions to avoid of having seizures at inappropriate times, public places or social events.

Therefore, the management of epilepsy should be aimed at controlling seizures and improving patient's community life. Public educational programs should be conducted in order to raise awareness of the general public regarding the existence of effective therapy and eliminate the stigma of epilepsy.

DIAGNOSIS

Epilepsy is considered as fourth most prominent neurological disorder in the world that can affect people of all age groups. Exactly knowing if a person is having an epileptic seizure and diagnosing the type of seizure or epilepsy syndrome can sometime be difficult. And, since seizures rarely happen in a doctor's office, the information given to the doctor and other health care professionals by you or other witnesses is extremely important. Since the treatment of seizures depends on an accurate diagnosis, making sure that a person has epilepsy and knowing what kind is a critical first step. The diagnosis of epilepsy requires a thorough history about the semiology of the event and is aided by electroencephalography (EEG).

EEG has an important role in the diagnosis and classification of epilepsy. It can also provide information for predicting the response to anti-seizure drugs and to identify the surgically remediable epilepsies.It can give a lot of information about where the seizure is originating and how it is propagating in the brain.

EEG is an important test for diagnosing epilepsy because it records the electrical activity of the brain. It is safe and painless. The abnormal waveforms include spikes, sharp waves, and spike-and-wave discharges. Spikes, sharp waves along with slow waves in a specific area of the brain, such as the left temporal lobe, indicate that focal seizures might possibly come from that area. Primary generalized epilepsy, on the other hand, is suggested by spike-and-wave discharges that are widely spread over both hemispheres of the brain, especially if they begin in both hemispheres at the same time.

Unfortunately, EEG, although is the principal diagnostic test for epilepsy diagnosis, is a passive measure of cortical activity, and epileptiform discharges are usually sporadic events. Consequently, the sensitivity of a single EEG is only 29-55% [18-21], and 8% of patients will never have interictal discharges [22,23]. I would make sure these references are accurate.

This turns out to be especially challenging when bearing in mind epilepsy mimics such as psychogenic non-epileptic seizures (PNES), cardiogenic syncope, breath holding spells, stereotypies and recurrent dystonias/tremors. PNES are caused by a psychopathological process and consist of paroxysmal behavioral changes that resemble an epileptic seizure but are not associated with electrophysiological epileptic changes. They and are primarily diagnosed by history and video-EEG.

Moreover, interictal discharges are seen in up to 12% of patients without epilepsy [24,25].Therefore, in some cases, an EEG may be carried out while you are asleep (sleep EEG) or you may be given a small, portable EEG recording device to monitor your brain activity over 24 hours (ambulatory EEG).

Activating procedures like photic stimulation, hyperventilation and sleep deprivation are used to activate both interictal discharges and seizures. Photic simulation is useful for activation of generalized epileptiform discharges Hyperventilation is particularly useful for primary generalized epilepsies; however, it can also activate focal epileptiform discharges in up to 10% in partial epilepsies [27]. Several studies have documented that sleep deprivation can increase the chance of detecting epileptiform discharges in both partial and generalized epilepsies [26]. This is mainly

due to the effect of sleep deprivation and not the sleep per se. Activating procedures can increase the yield of detecting interictal epileptiform discharges.

Thus, EEG can neither rule in nor rule out the diagnosis in some situations. But still EEG is one of the most important tools for diagnosis of epilepsy. It helps in easy monitoring as well as proper management of neurological disorders. However, the visual perception of this complicated waveform analysis is not without difference of opinions and demands highly skilled interpreters for disease detection and diagnosis. Hence, an automatic detection and monitoring approach is desired in future perspectives. If parameters and features of EEG signals are extracted properly, then it can add great value in diagnosis process and patients can be saved from severe harms caused by sudden seizure attacks [29]. Accordingly, epileptic cases frequently experience deferrals in diagnosis and commencement of appropriate management. On the other hand, normal physiological discharges can be interpreted as epileptiform and the patient is unnecessarily started on a seizure medication.

EPILEPSY PREVALENCE:

In 2004, the world health organization (WHO) estimated that nearly 80% of the burden of epilepsy worldwide is borne by the resource-poor countries. In developed countries, the lifetime prevalence rate for epilepsy ranges from 3.5 to 10.7 per 1,000 person-years, and the incidence rate ranges from 24 to 53 per 100,000 person-years [18]. In recent systematic reviews, the lifetime prevalence rates for active epilepsy varied from 1.5 to 14 per 1,000 person-years in Asia, from 5.1 to 57.0 per 1,000 person-years in Latin America, and from 5.2 to 74.4 per 1,000 person-years in sub-Saharan Africa [19]. In developing countries, this figure is often close to twice as high due to the higher risk of experiencing conditions that can lead to permanent brain damage.

TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS)

A constant current stimulator and surface electrodes soaked in normal saline are required for tDCS. The former is the source of steady flow of 0-4 mA direct current and it continually monitors the resistance in the system. Saline soaked electrodes based onto the scalp over desired areas [(e.g. the left or right precentral gyrus region (corresponding to C3 or C4 of the International 10-20 EEG system)] make terminal relaying currents across the scalp and through the underlying brain tissue. tDCS is a noninvasive brain stimulation technique that induces polarity-dependent (anodal electrode increase excitability and cathode decrease excitability) alterations of cortical excitability.

Once turned on, the constant current stimulator generates a transient tingling sensation under the electrode which disappears in 30 sec to 1min thereby making it optimal for blinding subjects (in sham-controlled studies) by switching it off after the initial sensory experience. A previous study demonstrated that current densities 25 mA/cm2 did not damage brain tissue and the protocols where 1-2 mA current is administered fall within these limits [22]. Previous studies have argued that in spite of a fraction of the direct current being shunted through the scalp, tDCS carries enough currents to the underlying cortex, sufficient for neuronal excitability shifts [23]. Another study has also reported change in measures of cerebral blood flow in brain regions that are subjected to transcranial anodal direct current thereby proving that transcranially administered direct currents can affect tissue excitability as well as regional blood flow as an indirect indicator of change in regional tissue excitability [24].

The important properties that make tDCS advantageous over other non-invasive brain stimulation methods include its ease of use, its large electrode size allowing influence over a larger neural network, a sham mode allowing controlled experiments and randomized controlled clinical trials, and its portability making it possible to apply stimulation while the patient receives occupational/physical therapy. However, tDCS is limited because of its poor temporal resolution and anatomical localization. In addition, inter-individual variation in conductivity due to differences in scalp, hair, and bone composition can hamper the current that is transmitted to the brain. Moreover, single sessions and multi-day sessions have been done and found to be safe [25]. tDCS is being used in the epilepsy in different parts of the world.

Most of the studies use cathadoltDCS in 1 mA [21-25]. Most of the studies shows improvement in outcome (e.g. decrease the epileptic discharge in active groups). There is a defect in sample size, and we think we should do multi-research in larger sample size due to the huge improvement (e.g. Assenza G. 2014, only two subjects and show huge improvement which is not applicable. In general, tDCS is a good additional treatment to epilepsy + medical therapy which is the essential treatment until now.

ECONOMIC EFFECTS OF EPILEPSY

Economically, epilepsy has a huge effect, with almost 5% of the medical costs of industrialized countries given to the disease. Although in real terms morbidity is relatively low, the long-term impairments left behind are hugely detrimental both in terms of hospital and other care sector costs. In the past, the greatest prevalence of epilepsy has been in the developed countries, but a change in this pattern may be expected as more and more countries adopt a more Westernized way of life. The overall rate of epilepsy incidence in low and middle income countries exceed that than of high-income countries, by about 20%.

CONCLUSIONS

Epilepsy is one of the leading causes of death and neurological disability in adults, inflicting a heavy burden on affected individuals and their families. tDCS is a method for focal brain stimulation. tDCS is based on decades-old observations that neuronal firing is modulated by low amplitude electrical direct current (DC). Specifically, when applied to the cerebral cortex, cathodal DC inhibits neuronal firing [9, 10]. The mechanisms by which cathodal DC reduces neuronal firing likely relate to hyper-polarization of the soma membrane which occurs when the apical dendrites neuron are oriented toward the cathode in a constant electric field. The practical application of tDCS is simple: low amplitude DC is administered via scalp electrodes such that the cerebral cortex is exposed to cathodal DC beneath one of the electrodes, and the return (anodal) electrodes can be placed anywhere else on the body, or in more complex arrangements to minimize currents at any site. tDCS methods have also recently been adapted to rats for work with disease models [11-14]. Hundreds of tDCS trials have demonstrated the technique to be well tolerated and safe. Direct electrical current stimulation is presently FDA-approved for extracranial use, and FDA applications for cranial stimulation (tDCS) for management of mood disorder and chronic pain are in progress. tDCS units are also inexpensive and light-weight. The electrical supply can be derived from conventional 9-volt batteries. The scalp electrodes can be fastened in seconds. tDCS can be combined easily with other therapies, such as those that may be required for resuscitation of an acutely-injured patient. tDCS is presently under investigation as a treatment for epilepsy, where excess cortical excitability is a prominent feature of the disease process, and where neuronal inhibition may be beneficial. Thus for epilepsy, tDCS may offer a practical non-pharmacologic therapy for the large minority, approximately 35%, of patients whose seizure cannot be controlled by medication.

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Conflict of interest: Author declares no conflict of interest.
Funding disclosure: Nil

Author's contribution:
Abdulrahman Al-Thaqib; concept, data collection, data analysis, manuscript writing, manuscript review
Ali MirBaradi; data collection, data analysis, manuscript writing, manuscript review
RaidahSaleem;data collection, data analysis, manuscript writing, manuscript review
Shahid Bashir; concept, data collection, data analysis, manuscript writing, manuscript review