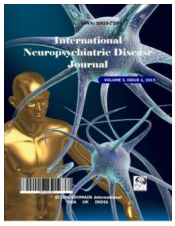

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Safety of Repeated Twice-daily 30 Minutes of 2 mA tDCS in Depressed Patients

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Authors' contributions

This work was carried out in collaboration between all authors. Authors UP and FP designed the study and wrote the protocol. Authors BL and WS performed the literature search and wrote the first draft of the manuscript with assistance from author AH. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: Transcranial direct stimulation (tDCS) is recently discussed as a therapeutic option in psychiatric disorders and has brought preliminary convincing results in the treatment of depressive disorders. Hence the optimal stimulation parameters still remain elusive as randomized controlled trials over last years used divergent stimulation protocols and duration, frequency, and current strength still have to be standardized.
Presentation of Cases: In this case series we report on the safety of twice daily 30 min tDCS at 2 mA over longer stimulation periods and interval treatment. Six patients (mean age 59.5±22.3, age range 29-87 years) with major depressive disorder received 20 to 31 tDCS treatments within 14 and 50 days, including acute treatment series and maintenance treatment. In the majority of participants, tDCS exerted antidepressant effects. tDCS was well tolerated and there were no clinically relevant adverse events.
Discussion: These preliminary data suggest safety and tolerability of twice-daily 30 min tDCS even in a prolonged protocol.
Conclusion: tDCS is gaining growing importance as a therapeutic tool in neuropsychiatric disorders and seems to be safe even when applied extensively.

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Keywords: Transcranial direct current stimulation; tDCS; safety; tolerability; twice-daily; 2 mA current strength.

1. INTRODUCTION

Transcranial direct current stimulation (tDCS) is being applied for the treatment of psychiatric disorders since a decade and has shown positive results in various disorders, i.e. in depressive disorders and to some extent in schizophrenia [1]. While early tDCS studies used in the clinical context applied 1 mA current strength and 15 min duration, recent studies showed that 2 mA and 2x20 min duration per day were safe [2,3]. The largest study up to now, the SELECT-TDCS trial by Brunoni et al. [4] used 10 treatments of 30 min within two weeks, followed by two maintenance treatments. In this large trial of 120 participants, no adverse events were observed. Recently, a study in patients with severe depression showed that twice-daily 30 min duration and 2 mA current strength were safely applied within 5 days of intervention [5]. Given a supposed dosage-related effect of tDCS, enhanced and prolonged stimulation protocols have to be evaluated.

Here, we report data on safety and tolerability of twice-daily 30 min and 2 mA tDCS in six patients who were treated with tDCS as an adjunct to psychopharmacotherapy in major depressive disorder. These patients received between 20 and 31 stimulations during acute and maintenance treatment, reaching from two up to seven weeks.

2. PRESENTATION OF CASES

The cases presented here are pilot patients prior to the beginning of a clinical trial for the treatment of major depressive disorders with a combined regimen of citalopram/escitaloprame and twice daily tDCS with a total number of 20 to 30 tDCS sessions. This so-called AzteK study ("Antidepressivum und zusätzliche transkranielle elektrische Kortexstimulation" – antidepressant and additional transcranial electrical cortex stimulation) was approved by the local ethics committee and was registered at the World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00008009)

All patients gave written and oral informed consent for an individual treatment with tDCS as an add-on to present medication in order to evaluate feasibility and tolerability of the tDCS protocol of the upcoming clinical trial. tDCS was applied with an Eldith DC-stimulator (neuroConn, Ilmenau, Germany). Saline-soaked sponge electrodes (35 cm^2) were positioned over the left and right dorsolateral prefrontal cortex (F3: Anode; F4: Cathode) as previously reported [4]. 2 mA tDCS was applied twice for 30 min within a 3 h interval in the morning. Clinical changes were measured with Clinical Global Impression (CGI), daily activities were measured with Global Assessment of Functioning (GAF).

2.1 Patient 1

The 29 year old patient was suffering from recurrent depressive episodes since he was 16 years old. Intermittent pharmacotherapy had no effect (venlafaxine) or had severe side effects (mirtazapine, bupropion). Upon admission, he presented a depressive syndrome for two months after discontinuing duloxetine four months before due to erectile dysfunction. The patient decided to restart duloxetine 90 mg in combination with 15 sessions of tDCS within 16 days. He showed a clear improvement of rumination, anhedonia, impetus, sleep and mood after two weeks. However, after discontinuing tDCS, he showed a severe relapse of depressive symptoms. Medication change to citalopram 40 mg showed no improvement and decision for a second tDCS series was made two weeks after end of first series. After 10 stimulations within 5 days the patient showed clear improvement of depressive symptoms and tDCS was discontinued. The patient only reported moderate side effects consisting in mild headache for a few hours after the first three tDCS sessions. GAF was 25 at admission, CGI 6. At discharge, GAF was 47 and CGI 4.

2.2 Patient 2

The 70 year old patient was suffering from a recurrent depressive disorders over 1 ½ years and was treated as an inpatient for one year including several antidepressant and augmentative regimen changes, a series of 20 acute treatments with electroconvulsive therapy (ECT) including maintenance ECT over weeks. Overall, treatment strategies including ECT series only exerted moderate and transient improvement, and the patient was transferred to

our service for tDCS. She presented a severe lack of impetus, depressed mood, anxiety, inner tension and akathisia. 20 tDCS treatments were applied within 14 days as an add-on to stable pharmacologic treatment, consisting in mocobemide, opipramol, and risperidone. The patient only showed modest improvement, however there was a light decline in inner tension and akathisia. Side effects of tDCS did not occur. GAF (25) and CGI (6) did not change during inpatient stay.

2.3 Patient 3

The 59 year old patient was suffering from a chronic depression over several years, presenting with sadness, senselessness of life, lack of impetus, and anhedonia. Over the past years, he was treated with St. John's wort, DHEA, testosterone, 5-HTP, and thyroxin. Medical history comprised no relevant somatic disorder. Admission followed the appearance of suicidal thoughts. Due to his concerns about a psychopharmacologic regimen, a series of 31 tDCS within 29 days was performed. Suicidal thoughts vanished, mood and impetus improved markedly, and the patient was able to maintain structure of daily activities as an outpatient and to restart working. Side effects comprised only mild tingling and itching sensation under the electrodes. GAF improved from 45 to 55, CGI from 5 to 4.

2.4 Patient 4

The 32 year old patient was suffering from recurrent depressive episodes since she was 16. Psychiatric history comprised two inpatient stays in the last 4 years, including several treatment regimen changes and a series of ECT. Upon actual submission, she presented a severe depressive syndrome since 4 months, although continuing her medication of venlafaxine, quetiapine, and lithium at stable doses. She preferred to continue her medication and agreed in a series of 30 tDCS within 21 days. She showed clear improvement of mood, impetus, anhedonia, and rumination. tDCS was tolerated without any side effect. CGI improved from 5 to 4 during hospital stay, GAF from 35 to 45.

2.5 Patient 5

The 50 year old patient was suffering from recurrent depressive episodes for 31 years. In her past medical history she was diagnosed with double depression and was treated with venlafaxine, quetiapine, buspirone, and zolpidem. Furthermore she received lisdexamfetamine for an attention deficit syndrome. Upon actual admission due to a depressive syndrome with suicidal thoughts, venlafaxine, buspirone, and lisdexamfetamine were replaced by tranylcypromine and amisulpride without improvement. Decision for ECT was set and the patient received a series of 12 bilateral ECT, followed by maintenance ECT for several weeks. Pharmacotherapy with tranylcypromine, quetiapine, and amisulpride was continued and the patient showed a clinical response after ECT. However, due to cognitive deterioration, maintenance ECT had to be stopped and a series of 10 tDCS was performed, followed by 12 maintenance tDCS over 6 weeks in an outpatient setting. During acute and maintenance tDCS, clinical improvement by ECT carried on. Except for light skin reddening, the patient reported no side effects. GAF improved from 45 to 65 and CGI from 6 to 3 during hospital and outpatient treatment.

2.6 Patient 6

The 87 year old patient was suffering from recurrent depressive episodes since four years with the leading symptom of nausea. During several inpatient stays over the past years, a variety of antidepressants, antipsychotics, anxiolytics, and hypnotics only had modest and transient effects on depressive symptoms. Upon admission, he presented with nausea, vertigo, depressed mood, and lack of impetus. Actual pharmacotherapy of moclobemide, mirtazapine, and aripiprazole was continued and the patient received 20 tDCS during inpatient stay and further 10 maintenance tDCS during over a 5 week outpatient stay. Nausea vanished completely during acute tDCS treatment, depressive symptoms improved and the patient remained stable during outpatient treatment. tDCS treatment showed no side effects. GAF increased from 35 to 55 during tDCS, CGI sank from 5 to 4.

3. DISCUSSION

In this case series with 6 patients (mean age 59.5±22.3, age range 29-87 years) we aimed at evaluating the safety and tolerability of repeated twice-daily tDCS under naturalistic conditions. Although this case series is limited due to heterogeneity of patient characteristics,

concomitant medication, treatment resistance and different treatment protocols (total number of tDCS and treatment intervals), it shows that twice-daily tDCS can be safely applied over longer treatment periods and that side effects are mild and transient, and do not exceed the side effects reported in previous studies, even when stimulating with enhanced protocols. Even in older patients, intensive tDCS was well tolerated without any adverse effects, as also previously reported [6]. tDCS treatment in higher dosage and increased total number of stimulations exerted promising effects in this mainly treatment resistant or chronically depressed patient sample. As there is growing evidence that tDCS has a dosage-dependent effect, i.e. in depressive disorders, there is a need for optimizing stimulation protocols in terms of amperage, duration, intervals between stimulations and total treatment duration.

4. CONCLUSION

tDCS has proven to be safe tool for neuromodulation and is currently evaluated in a variety of neuropsychiatric disorders. Over the past years, stimulation protocols were currently expanded in length and strength of application. It is likely that enhanced protocols are more effective without increasing the risk of adverse effects. There is a need for systematic investigation of new stimulation protocols.

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CONFLICT OF INTEREST

F.P. has received grants from neuroConn GmbH, Ilmenau, Germany. The other authors declare no conflict of interest.

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