TRANSCRANIAL DIRECT CURRENT STIMULATION FOR REFRACTORY AUDITORY HALLUCINATIONS IN SCHIZOPHRENIA: ACUTE AND 16-WEEK OUTCOMES

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Introduction

Peripheral neurostimulation techniques such as rTMS curtails disabling symptoms such as refractory auditory hallucinations in schizophrenia by modulating abnormal cortical activity. However, effects are transitory & nonspecific[1]

tDCS results in prolonged hyperpolarization of cerebral cortex underlying the cathode & prolonged depolarization of cortex underlying the anode

Effects analogous to cortical inhibition & excitation associated with low & high-frequency rTMS, respectively with greater convenience & at less expense .[2]

Evidence for efficacy of tDCS in refractory AH rests only on few studies [3]

Given that cathodal tDCS exert effects similar to rTMS, it is conceivable that tDCS may be a simpler alternative to rTMS for patients with refractory AH

Objectives

To assess the efficacy of tDCS in refractory AH

To assess the impact of tDCS on negative symptoms in schizophrenia

Material and Methods

Venue - IQRAA International hospital and Research Center, Kozhikode, Kerala, India

Sample- Consecutive 31 patients with DSM-5 diagnosis of schizophrenia with refractory AH

Study approved by IEC & provided written informed consent

Patients maintained on same treatment throughout study period Study duration - 4 months

Two sessions per day (5-6 hours apart), given daily for 2 weeks Followed up after 2 weeks & then monthly for the next 3 months

Clinical rating done at morning before tDCS administration tDCS administration & clinical rating assessed separately by different investigators

tDCS administration

Indigenous device - Zeebeetronics, Bangalore, India

Anode over left DLPFC & cathode between T3 & P3 based on 10-20 electroencephalogram electrode positioning system

1-3 mA current passed through about 25-35 cm square metalgauze saline-soaked electrodes for 30 min per session

Inclusion Criteria: Age, 18-60yrs; Men & Women; Medication-refractory AH for at least past 3 months; No exposure to ECT at least 6 months before participation in study

Exclusion Criteria: Any medical/psychiatric condition that may interfere with understanding of patient in the administration of protocol; Concomitant alcohol or substance abuse

Outcome Assessment

Auditory Hallucinations Rating Scales (AHRS1)

Auditory Hallucinations Rating Scales (AHRS2)

Positive and Negative Syndrome Scale (PANSS)

Adverse events - SAFTEE checklist of adverse effects

Statistical analysis

Comparison of individual items score - Friedman's test

LOCF analysis of total score & individual items score -one-way RMANOVA

Predictors of response -correlation

Comparison of improvement in hallucination between males & females - Man-Whitney

LOCF analysis of PANSS negative symptoms -one-way RMANOVA

The significance threshold was set at 0.05

Results

Sample disposition - Out of 31 patients 13 did not complete study

Sample description - Mean age: 35.8 ±11.6 years

Mean education: 10.7 ± 3.4 years : Mean age at onset of illness: 24.2 ±12.3 years

54.8% males, 41.9% married, 35.5% living in a joint family, 71% unemployed

Table -1 Mean (SD) auditory hallucinations rating scale total scale scores using AHRS1&AHRS2

	AHRS1 (n=31)	AHRS2 (n=31)
Baseline	30.3 (5.1)	30.3 (5.3)
Week 1	25.0 (9.6)	26.0 (9.5)
Week 2	21.5 (10.4)	22.7 (10.4)
Week 4	21.5 (9.6)	23.0 (10.2)
Week 8	20.8 (9.6)	22.7 (10.5)
Week 12	19.2 (9.8)	20.3 (10.7)
Week 16	18.5 (9.6)	20.0 (10.3)

Significant attenuation of scores for AHRS1 (F=8.31, df=6,25, P<0.001) & AHRS2 (F=5.50, df=6,24, P<0.001). For AHRS1, 29% reduction in total score at the end of week 2 & a further 10% improvement thereafter; thus, at the end of 4 months, there was a total of 39% improvement

For AHRS2, 25% reduction in total score by the end of week 2 & a further 9% improvement thereafter; thus, at the end of 4 months, there was a total of 34% improvement

Comparison of mean individual item scores in AHRS1 showed significant improvement in each item of AHRS1 with bulk of improvement apparent by end of week 2. Comparison of mean individual item scores in AHRS2 showed improvements apparent in each item except location, belief& disruption; again, bulk of improvement apparent by end of week 2

By the end of study, on AHRS1 & AHRS2, 16.1% patients had complete remission&51.6% & 45.2% responded respectively

No significant correlation between patient age &improvement on AHRS1 (r=0.06) or AHRS2 (r=-0.01)

M(SD) improvement in AHRS1 was 11.7(12.0) vs 12.0(7.8) in men vs women, respectively (Mann-Whitney z=0.80, P=0.43)

M(SD) improvement in AHRS2 was 10.9(12.0) vs 9.2(7.6) in men vs women, respectively (Mann-Whitney z=0.10, P=0.92). Thus, no moderators of response were identified.

Comparison of mean score of negative symptoms from baseline to 16th week showed very small (11%) but statistically significant improvement in PANSS-N score (F=4.25, df=6.2, P=0.005)

Discussion

Our open clinical trial tDCS reduced severity of refractory AH - after 28 sessions over 2 weeks, 29% reduction in severity of AH, effect maintained up to 16 weeks

At the end of trial, 38.9% still be categorized as responders (defined as a ≥30% reduction in AHRS score)

Our results in conformity with previous reports on use of tDCS in refractory AH in schizophrenia[3]

Long-lasting effect could not be explained by changes in medication, as all patients maintained on same medications throughout the study period

No AEs except occasional intra-session tingling at the electrode site

Beneficial effect not restricted to only AH -Significant reduction in negative symptoms

Previous studies showed association between negative symptoms &DLPFC hypoactivity[4]

Cathodal tDCS induced prolonged hyperpolarization & anodal tDCS induced prolonged depolarization- analogous to inhibition & stimulation associated with low & high frequency rTMS, respectively

tDCS reduces negative symptoms by activation of DLPFC & correcting hypofrontality or fronto-limbic imbalance[5]

Effects on AH could be the result of cathodal tDCS at the temporo-parietal junction acting on temporo-parietal hyperactivity

It is possible that tDCS may do what rTMS does but with greater convenience & at less expense

Observed effect may probably a result of combination of local impacts of two electrodes & their distant repercussions

Hypothesis of a dysfunctional fronto-temporal connectivity frequently been mentioned in neuroimaging studies to explain positive symptoms, especially AH[6]

Conclusions

tDCS - easy-to-use, low-cost stimulation tool with few side effects

New tool in the treatment of refractory symptoms

Domiciliary treatment feasible, but regular checks necessary to ensure adherence to stimulation protocols

Future studies with larger samples & additional evaluations, such as functional evaluations & imaging needed to confirm these promising results

References

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