

Statistical Analysis Plan (SAP)

09/02/2012

Date

“Triple site” transcranial magnetic stimulation for the treatment of chronic tinnitus: Outcomes from an open-label pilot study in comparison with former data of single site stimulation

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1. Research question

Is a triple site stimulation protocol (consisting of high frequency rTMS of left prefrontal cortex plus low frequency rTMS of left and right temporoparietal cortex) more effective than a standard single-site low frequency rTMS of left temporal cortex (treatment: 10 sessions on 10 consecutive working days)? Data for triple site stimulation were collected in an one-arm open-label study. Data for single site stimulation are taken from a former study which used this stimulation protocol as control treatment. Analysed time points are screening, baseline, day 12 (final visit) and day 90 (follow-up).

Inclusion criteria for triple site stimulation:

- age: older than 18 years
- subjective chronic tinnitus
- duration: more than 3 months

Exclusion criteria for triple site stimulation:

- contraindication for rTMS (epilepsy, cardiac pacemaker, head injury, evidence of significant brain malformation or neoplasm, cerebral vascular events, neurodegenerative disorder affecting the brain or prior brain surgery, metal objects in and around the body that cannot be removed, pregnancy)
- objective tinnitus
- treatable cause of the tinnitus
- involvement in other treatments for tinnitus at the same time
- clinically relevant psychiatric comorbidity
- clinically relevant unstable internal or neurological comorbidity
- alcohol or drug abuse
- prior treatment with TMS

Inclusion criteria for single site stimulation:

- age: older than 18 years
- subjective chronic tinnitus
- duration: more than 3 months

Exclusion criteria for single site stimulation:

- contraindication for rTMS (epilepsy, cardiac pacemaker, head injury, evidence of significant brain malformation or neoplasm, cerebral vascular events, neurodegenerative disorder affecting the brain or prior brain surgery, metal objects in and around the body that cannot be removed, pregnancy)
- objective tinnitus
- treatable cause of the tinnitus
- involvement in other treatments for tinnitus at the same time
- clinically relevant psychiatric comorbidity
- clinically relevant unstable internal or neurological comorbidity
- alcohol or drug abuse
- prior treatment with TMS

2. Category of research question according to the SOP TRI-SA.

- 1. Efficacy analyses of specific treatments
- 2. Conceptual questions, e.g., psychometric performance of outcome instruments or interrelations among assessment instruments
- 3. Interrelations between clinical or demographic characteristics
- 4. Examination of prognostic factors for treatment success
- 5. Ad hoc research questions, i.e., issues that arise out of new findings or conceptualizations in tinnitus research

3. Description of the dataset used for the analysis

- Dataset from the default data import at DD/MM/YYYY, including n=XXXX patients
- Center specific dataset import at 27/01/2012, including n=82 patients

4. Variables used in this analysis

- demographic variables: gender, Age_in_years
 - clinical characteristics: laterality, duration, average of AudioMLeft125_screen to AudioMRight8k_screen (mean hearing level in dB HL for the frequencies 125 to 8000 Hz)
 - tinnitus questionnaires: THI_totalscore_screen to THI_totalscore_final (tinnitus handicap inventory), BDI_totalscore_screen to BDI_totalscore_final (Beck depression inventory), TF_totalscore_screen to TF_totalscore_final (tinnitus questionnaire)
 - numeric rating scales: Tinnitusatpresent_screen to Tinnitusatpresent_final, Strongloud_screen to Strongloud_final, Uncomfortable_screen to Uncomfortable_final, Annoying_screen to Annoying_final, Ignoring_screen to Ignoring_final, Unpleasant_screen to Unpleasant_final (how much of a problem, how strong or loud, how uncomfortable, how annoying, how easy is it to ignore, how unpleasant is tinnitus)
 - global clinical assessment: CGI_V1, CGI_V2, CGI_final
 - group variable: treatment 1033 (triple site stimulation) and treatment 1009 (temporal stimulation)
- included visits are screening, baseline, final visit (depending on treatment code "V1" or "V2"), and follow-up visit after three months ("final")

5. Statistical methods

- descriptive statistics of the clinical and demographic variables
- missing values: last observation carried forward or backward
- primary outcome (treatment effect): ANOVA with within-subjects factor time (baseline vs. final visit) and with between-subjects factor group (triple site vs. temporal group) with according post-hoc Student t-tests for TQ
- secondary outcome: ANOVA with within-subjects factor time (screening, baseline, day 12, day 90) and with between-subjects factor group (triple site vs. temporal group) with according post-hoc Student t-tests for TQ, THI, BDI and numeric rating scales

6. Planned start and end of analysis

- Start of analysis: 02/2012
- End of analysis: 02/2012

7. Literature

European Medicines Agency (2001). *ICH Topic E 10. Choice of Control Group in Clinical Trials*. Retrieved 09.02.2012, from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf