A New Approach to Treating Acute Ischemic Stroke in Human Brain: Pulsed ElectroMagnetic Fields

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INTRODUCTION

A large number of studies explored the biological effects of extremely low-frequency magnetic fields (ELF-MFs) and reported the induction of functional changes in excitable biological tissues such as nervous, muscular and cardiac tissues which had exposed to fields with an amplitude of the order of up to a few milliTesla. Neurophysiological studies described measurable changes in brain electrical activity following low-intensity ELF-MF exposure and suggested that they can influence neuronal functions such as motor control, sensory perception, cognitive activities, sleep and mood. Varani et al. [1] found that pulsed ELF-MFs (75 Hz; 1.5 mT) produce a specific increase in density and functionality of adenosine receptors (A2A) expression in rat cerebral cortex and cortical neurons. The neuroprotective potential of pulsed ELF-MF has also been confirmed in animal models of brain ischemia. Grant et al. have evaluated the effects of pulsed ELF-MF on cerebral damage in a rabbit model of transient focal ischemia. They found that the exposure to pulsed ELF-MF immediately after the onset of ischemia, attenuated cortical edema on Magnetic Resonance Imaging (MRI) and reduced neuronal damage as shown by histological examination [2]. Interestingly, Capone et al. [3], using ELF-MF with identical field characteristics of the one investigated in the Varani’s studies, showed in healthy volunteers an increase in intracortical facilitation produced by paired pulse transcranial magnetic stimulation (TMS) with no side effects.

The purpose of this safe efficacy Phase I study is the validation of pulsed ELF-MF stimulation as non-invasive and safe tool to promote recovery in acute ischemic stroke patients.

MATERIALS AND METHODS

This is an open label, one arm, and dose escalation exploratory study aiming at evaluating the safety of pulsed ELF-MF stimulation in acute ischemic stroke. Inclusion criteria comprised: age>18; first onset, mono-hemispheric ischemic stroke; onset of symptoms within 48 hours; National Institutes of Health Stroke Scale (NIHSS) score >4; patient was to be alert, medically stable and able to follow simple verbal commands; signed written informed consent. A cohort of 9 patients were to be stimulated with three different doses pulsed ELF-MF (75 Hz, 1.5 mT) for 5 consecutive days, starting within 48 hours from the onset of the stroke. The first 3 patients enrolled were treated for 45 min/day. In the absence of observed Adverse Events (AEs), the following 3 patients were treated for 120 min/day and, if AEs were not observed, the last 3 patients were treated for 240 min daily. The primary outcome (safety endpoint) was evaluated by the incidence of adverse events and mortality throughout the stimulation period and after 1-year follow-up. Change from baseline of clinical and radiological scores was used as secondary outcomes. Patients were examined by MRI (1.5 Tesla). The following brain MR sequences were collected: axial plane T1w-SE, Fluid-Attenuated Inversion Recovery (FLAIR), and Diffusion-Weighted Imaging (DWI) with Apparent Diffusion Coefficient (ADC). The neuroradiologist measured the ischemic lesion volume (ILV) through the MIRcro software. Change (Δ) in ILV was determined by MRI; ΔILV is defined as ILV measured by FLAIR sequence at 30 days after pulsed ELF-MF treatment minus the initial ILV measured by DWI trace sequence before pulsed ELF-MF treatment.
RESULTS

Until now six patients have been recruited; 5 patients completed 12 months follow-up. No adverse events have been reported. A dose-response effect has been find in the reduction of ischemic area evaluated by magnetic resonance at 1month follow-up (Figure 1). The clinical outcome of all patients has been enhanced at each follow-up.

![Infarct Growth Increase](image)

Figure 1. Infarct growth increase (FLAIR/DWI ratio) after 45 minutes and 120 minutes of PEMF exposure.

CONCLUSIONS

In agreement with experimental data, this finding suggests that probably the modulation of neurotransmitters receptors such as adenosine A2A might represent a possible explanation for the effect of ELF-MF. This pilot study was designed to investigate the safety, tolerability and effectiveness of pulsed ELF-MF in patients with acute ischemic stroke and the preliminary results suggest that ELF-MF stimulation is safe. In conclusion, considering the effects of such fields on several brain functions, there is great interest about the ELF-MFs potentialities in the treatment of neuroprotection. A multicenter, prospective, randomized and double-blind study has been planned to evaluate the efficacy of the treatment. This project aims at providing an innovative neuroprotective strategy, in which unconventional non-invasive brain stimulation will be tested as an alternative approach to drugs.

REFERENCES