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

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Pulsed ElectroMagnetic Fields

- Orthopaedic setting for bone regeneration and cartilage repair
- Model of peripheral/terminal vascularization

**Free flap:**


**Myocardial infarct:**


**Brain:**

Skin flap in Rats

Adult male rats underwent full-thickness skin incision along the dorsal midline and were divided into 3 groups:
• Control
• PEMF 4 hour/die
• PEMF 24 hours/die

Wound tensile strength of the dorsal incision were tested.

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<th>Tensile Strength</th>
<th>Flap Length</th>
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<tr>
<td>Control</td>
<td>3.6 ± 0.47</td>
<td>2.88 ± 0.26</td>
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<tr>
<td>4 hours/die</td>
<td>4.65 ± 0.81</td>
<td>2.9 ± 0.29</td>
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<tr>
<td>24 hour/die</td>
<td>4.77 ± 1.32</td>
<td>3.73 ± 0.42</td>
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Flap survival was found to be significantly enhanced in animal treated with PEMF and a dose-response effect.

Johnson DJ. et al. 1987
Myocardial Infarcts in Rats

In three hundred forty male Wistar rats the anterior descending branch of the left anterior descending artery (LAD) was ligated at the level of the third proximal segment.

Animals were exposed to PEMFs for the length of the experiment (18h).

Albertini G. et al. 1999
N, necrotic area; V, viable myocardium.

Myocardium slice B of rat exposed to PEMF

area of particulate fluorescence is the perfused myocardium

Albertini G. et al. 1999
Focal cerebral ischemia in rabbit

12 Rabbits (6 stimulated, 6 sham treated) underwent transorbital clip occlusion of the left internal carotid, proximal left anterior cerebral and proximal left middle cerebral arteries × 2h, followed by 4h of perfusion.

10 min following arterial occlusion rabbits were exposed to PEMF × 6 hours (2hs of arterial occlusion + 4hs of arterial perfusions)

The exposure to PEMF

Grant G. et al. 1994
MRI & HISTOLOGIC EXAMINATION
ANTERIOR LEVEL – CORONAL LEVEL I

PEMF

Control

Grant G. et al. 1994
Preliminary results suggest:

PEMF may improve the local cerebral blood flow at the microcirculatory level.

However, the mechanism by which PEMFs exert their protective effect was not clear.

One could suppose that the PEMFs, in the acute stage:

- limit the inflammatory response
- limit the local edema
- favor microcirculation recovery
Effect of low frequency electromagnetic fields on $A_{2A}$ adenosine receptors in human neutrophils

Varani K. et al. 2002
Effect of Pulsed Electromagnetic Field Exposure on Adenosine Receptors in Rat Brain

Varani K. et al. 2011

Whole brain

Rat brain membranes

Cortical neurons
Twenty-two (9 male and 13 female) healthy volunteers [mean age 27.6 ± 9 (SD) years] participated in the study. In 14 of the subjects we also evaluated the effects of sham field exposure. After 45 min of PEMF exposure, intracortical facilitation was evaluated.

The pulse generator (B-01; IGEA, Carpi, Italy) supplied the coil with a single-pulsed signal at 75 ± 2 Hz, with a pulse duration of 1.3 ms. The peak intensity of the magnetic field was 1.5 ± 0.2 mT.
Intracortical excitability

PEMFs exposure may produce an enhancement in cortical excitatory neurotransmission, with an increase of about 20%.

Capone F. et al. 2009
The trial is registered on clinicaltrials.gov (NCT01941147).
Material and Methods

Design:
open label, one arm, non randomized, dose escalation.

Patient population
Nine patients were recruited from in-patient unit of the Neurology Department of Polyclinic Campus Bio-Medico of Rome

Inclusion criteria:
age > 18; first onset, mono-hemispheric ischemic stroke; onset of symptoms within 48 hours; National Institutes of Health Stroke Scale (NIHSS) score > 4; patient is alert, medically stable and able to follow simple verbal commands; signed written informed consent.

Exclusion criteria:
acute intracranial hemorrhage; previous ischemic or hemorrhagic stroke; history of seizure; contraindications to transcranial magnetic stimulation (such as implanted metallic parts of implanted electronic devices or other metal in body); life expectancy < 3 months; other serious illness or complex diseases that may confound treatment assessment; women known to be pregnant, lactating or having a positive or indeterminate pregnancy test; simultaneous participation in another study.
45 min
3 patients → No AE → 120 min
3 patients → No AE → 240 min
3 patients

Brain MRI

Neurological assessment: mRS, NIHSS, BI

Day1 Day2 Day3 Day4 Day5

Safety assessment: AEs, SAEs, mortality, vital parameters monitoring

Visit at 5 days
Visit at 30 days
Visit at 90 days
Visit at 365 days

Screening
within 48 hours from stroke onset

Treatment
5 consecutive days at increasing daily exposure (45, 120, 240 min)

Follow-up
Safety assessment: AEs, SAEs, mortality
Neurological assessment: mRS, NIHSS, BI

Capone F. et al. 2014
Primary outcomes:
safety
the incidence of AEs, severe AEs (SAEs)
mortality throughout the stimulation period and along 1-year follow-up.

Questionnaires on AEs will be administered daily during the whole hospitalization and, after the discharge, at each outward control.

Secondary outcome:
preliminary evidence of efficacy

Clinical outcomes and FU
NIHSS score, Modified Rankin Scale (mRS) score and in the Barthel Index (BI)
Immediately, 30, 90 and 365 days after pulsed ELF-MF treatment.
Neuroradiological outcomes

Patients were examined by MRI using an Achieva 1.5 T scanner

MR sequences:
- Axial plane T1w- SE, Fluid-Attenuated Inversion Recovery (FLAIR)
- Diffusion- Weighted Imaging (DWI) with Apparent Diffusion Coefficient (ADC)
- Ischemic lesion volume (ILV)

Change ($\Delta$) in ILV determined by MRI.

$\Delta$ILV 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.

**RED:** DWI in acute before PEMF

**Blue:** FLAIR @30 days after PEMF

**Violet:** overlapping → core of stroke

FLAIR-DWI = infarct growth

Capone F. et al. 2014
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 found in the reduction of ischemic area evaluated by magnetic resonance at 1 month follow-up

Capone F. et al. 2014
Interventi a favore della ricerca industriale delle imprese operanti nelle filiere maggiormente coinvolte dagli eventi sismici del maggio 2012 – art. 12 DL 74/2012

Nuovo dispositivo medico a campi magnetici Igea per Neuroprotezione nell’Ischemia Cerebrale: I-NIC

PHASE III – LEVEL I

A multicenter, prospective, randomized and double-blind study
Conclusions

• Pre-clinical finding suggests that the modulation of neurotransmitters receptors such as adenosine A$_{2A}$ might represent a possible explanation for the effect of PEMF.

• The pilot Fase I study suggests that PEMF stimulation is safe.

• The multicenter RCT aims at providing an innovative neuroprotective strategy, in which unconventional non-invasive brain stimulation will be tested as an alternative approach to drugs.
Thank you for your attention