Bilateral vs. unilateral transcranial magnetic stimulation of the primary motor cortex to treat chronic orofacial pain: a pilot study with a randomized controlled design

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Headaches
Study type	Interventional

Summary

ID

NL-OMON44200

Source
ToetsingOnline

Brief title
BvU-TMS

Condition

- Headaches

Synonym
facial pain, Trigeminal neuropathy

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Analgesic effect, Orofacial pain, Transcranial magnetic stimulation, Treatment

Outcome measures

Primary outcome

Primary Objective: Exploring whether bilateral MCS by TMS can provide a greater pain relief as compared to unilateral TMS of the MCS. This will be based on 1) the pain intensity scores before and during the experiment and 2) changes in quality of life during the experiment as measured by the McGill Pain Questionnaire.

Secondary outcome

Secondary outcomes of this study will be the experiences of the patients of the experimental period as obtained by interviewing the participants.

Study description

Background summary

In the early 1990*s, Tsubokawa and colleagues tried to provide a more effective treatment for thalamic pain syndromes. All forms of therapy, including deep brain stimulation (DBS) of the thalamic relay nucleus, were able to provide a pain relief of 20-30% in patients suffering from thalamic pain syndromes. Therefore, Tsubokawa and his group stimulated multiple brain regions in cats after a lesion of the spinothalamic pathway was induced. Outcome measurements of the pain control were blood flow of the thalamus and cerebral cortex, increased skin temperature of the painful area and improved movements of the affected limbs. They presented that chronic motor cortex stimulation (MCS) was most effective in treating thalamic pain syndromes [2]. After their first results, Tsubokawa*s group introduced MCS into clinical care [2-5]. Over the

years, various reports were published and more indications for MCS were introduced and tested [5-40]. In order to test new hypothesis and investigate the possible effects of MCS, transcranial magnetic stimulation (TMS) of the primary motor cortex has been introduced in 1995 [41]. The main indications for MCS today are 1)central post-stroke pain (including thalamus syndrome), 2)neuropathic orofacial pain, 3)phantom limb pain and 4)peripheral plexus avulsion [36, 40].
The underlying mechanisms of action of MCS remain largely elusive, other than that brain areas distant to the site of stimulation show to be involved. One of the mechanisms that has been describes discusses the release of a variety of neurotransmitters [42-53].
Other mechanisms concern descending volleys in the spinal cord [50, 51, 54]. In order to explain these widespread effects of MCS, the activation of stellate interneurons in the fourth layer of the cerebral cortex must be assumed.[55-57] These thalamocortical afferent fibers from C-type cells do not take part in the corticospinal tract, but connect subcortical structures and circuits to cortical areas [58-61]. Next to these neuroanatomical substrates, corollary discharges have been investigated as well. It has been discussed that sensory feedback comes from the peripheral nerves, the visual input, but also from the motor cortex itself. Therefore, a possible mechanism of action of MCS might be these corollary discharges which counterbalances the other feedback deficiencies[62]. Although several clinical trials showed a significant difference in analgesic effects between sham and active stimulation of the primary motor cortex[63-65], the placebo effect is also hypothesized to play a role in pain relief [62, 66].

Although the aforementioned mechanisms seem to spread throughout the entire nervous system, the thalamus that lies contralateral to the site of stimulation seems not to be affected. However, in 2016, Henssen et al. discuss that orofacial pain may be conducted in a bilateral fashion, inducing activation of both thalami [1]. For this reason, bilateral stimulation of the motor cortex is thought to induce a stronger analgesic effect compared to unilateral MCS.

Before starting to implant two electrodes into the epidural space of pain patients, further empirical researches that investigate the effects of bilateral stimulation of the primary motor cortex must be conducted. A non-invasive method of brain stimulation is called transcranial magnetic stimulation (TMS) in which electromagnetic coils held against the scalp influence underlying cortical firing. This method of investigation is non-invasive and safe and can help further exploration of cortical targets for neuromodulation for the treatment of pain [67].

Study objective

In 2016, Henssen et al. discuss that orofacial pain may be conducted in a bilateral fashion, inducing activation of both thalami [1]. For this reason, bilateral stimulation of the motor cortex is thought to induce a stronger

analgesic effect compared to unilateral motor cortex stimulation by transcranial magnetic stimulation. This study aims to investigate the superiority of bilateral transcranial magnetic stimulation (TMS) over unilateral TMS of the motor cortex

Study design

For this study, we aim to include approximately 12 patients with intractable, chronic orofacial pain of peripheral origin with a baseline NRS of at least 5 (0= no pain, 10= worst possible pain). The investigator (Dylan Henssen) contacts the pain nurse, neurosurgeons and pain physicians to ask them to seek contact with their patients to inform them about this research. Afterwards, if the patients wish to learn more or wish to participate, they receive an information package, including an information letter and an informed consent form. When the patient agrees to be included they receive four McGill Pain questionnaires which must be filled in weekly. After these four weeks, the patient is invited to the outpatient clinic to meet with the investigator. During this consultation, the patient talks about the pain he/she experiences, submits the four filled-in questionnaires and receives further information about the research. After the consultation, all patients are randomized in double-blinded fashion.

At the next meeting at the Donders Institute at Nijmegen, the patient takes place in a relaxing chair. A second, independent researcher will install the transcranial magnetic stimulation (TMS) coils, one on each side of the patient. The coils are positioned in such a fashion that both the coils can stimulate the primary motor cortex. Then the independent researcher starts the stimulation protocol. In the first session, the patient either receives unilateral or bilateral stimulation. After this session, the patient fills in a new McGill Pain questionnaire in order to measure the pain sensation after the first session of TMS. Then the patient goes home for one month. At home, another 4 McGill Pain Questionnaires are asked to fill in. After this, the patient returns to the Donders Institute to take place in the relaxing chair in order to be treated in the second session. Again, the patient either receives unilateral or bilateral stimulation, depending on what was received during the first session. Again, the patients are asked to fill in 4 new McGill Pain questionnaires, one per week (See figure 1).

At the end of this session, the patient is invited to meet with the investigator or independent researcher once more to talk about their experiences and pain relief during the research. This interview takes place at Radboudumc and is audio recorded.

All the McGill Pain questionnaires are analyzed by the researcher (Dylan Henssen) using SPSS. Afterwards, the independent researcher discloses which patient received uni- or bilateral in which order. The audio recorded

interviews are transcribed verbatim and analyzed using Atlas.tii.

Intervention

Transcranial magnetic stimulation (TMS)

Study burden and risks

Invested time is expected to be approximately 6 hours
Adverse effects are minimal, primarily headaches.
Single provoked seizures are very rare (<1 in 10.000)

Contacts

Public
Radboud Universitair Medisch Centrum

Geert Grooteplein 2
Nijmegen 6525 EZ
NL
Scientific
Radboud Universitair Medisch Centrum

Geert Grooteplein 2
Nijmegen 6525 EZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Untreatable pain in the orofacial region

Exclusion criteria

Intracranial neuromodulation device

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-03-2018
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	14-11-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	30-01-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL62849.091.17