The role of active stimulation in patients that have benefited from the long-term effects of MCS in the treatment of orofacial pain

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Is active stimulation still necessary in patients that suffer from chronic orofacial pain who have been successfully treated with MCS for over 4 years or is the analgesic effect caused by permanent axonotmesis?

Ethical review	Approved WMO
Status	Will not start
Health condition type	Headaches
Study type	Observational non invasive

Summary

ID

NL-OMON45382

Source
ToetsingOnline

Brief title
The role of active stimulation of MCS

Condition

- Headaches

Synonym
Trigeminal neuropathy; Facial pain

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: Motor Cortex Stimulation, Orofacial Pain

Outcome measures

Primary outcome

Pain scores, pain dimensions, Quality of Life, daily intake of pain medication

with use of the McGill Pain Questionnaire (Dutch Version) and qualitative

exploration of their experiences with use of interviews.

Secondary outcome

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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 (Tsubokawa, Katayama, Yamamoto, Hirayama, & Koyama, 1991). After their first results, Tsubokawa*s group introduced MCS into clinical care (Katayama, Tsubokawa, & Yamamoto, 1994; Tsubokawa et al., 1991; Tsubokawa, Katayama, Yamamoto, Hirayama, & Koyama, 1993; Yamamoto, Katayama, Hirayama, & Tsubokawa, 1997). Over the years, various reports were published and more indications for MCS were introduced and tested (Brown & Barbaro, 2003; Canavero & Bonicalzi, 1995, 2002, 2007; Carroll et al., 2000; Ebel, Rust, Tronnier, Boker, & Kunze, 1996; Fontaine, Hamani, & Lozano, 2009; Garcia-Larrea et al., 1999; Herregodts, Stadnik, De Ridder, & D'Haens, 1995; Hosomi et al., 2008; Im, Ha, Kim, & Son, 2015; Katayama, Fukaya, & Yamamoto, 1998; Katayama et al., 2001; Katayama, Yamamoto, Kobayashi, Oshima,

& Fukaya, 2003; Lazorthes, Sol, Fowo, Roux, & Verdie, 2007; Lefaucheur, Menard-Lefaucheur, Goujon, Keravel, & Nguyen, 2011; Louppe et al., 2013; Mertens et al., 1999; Mogilner & Rezai, 2001; Nguyen et al., 1997; Nguyen et al., 1999; Nuti et al., 2005; Peyron et al., 1995; Pirotte et al., 2005; Rainov, Fels, Heidecke, & Burkert, 1997; Roux, Ibarrola, Lazorthes, & Berry, 2001; Saitoh et al., 2001; Saitoh et al., 2003; Saitoh et al., 2000; Smith et al., 2001; Sokal et al., 2015; Sol et al., 2001; Son, Kim, Moon, & Kang, 2003; Tani, Saitoh, Hirata, Kato, & Yoshimine, 2004; Tirakotai et al., 2004; Yamamoto et al., 1997). 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 (Fontaine et al., 2009; Sokal et al., 2015).
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. The opioidergic system seems of great importance, as MCS is thought to modulate the descending volleys towards the PAG and related nuclei (de Andrade, Mhalla, Adam, Texeira, & Bouhassira, 2011; Fonoff et al., 2009; Maarrawi et al., 2007, 2013; Pagano et al., 2012). Activation of the striatal dopaminergic system seems to be involved as well (Strafella, Paus, Barrett, & Dagher, 2001; Strafella, Paus, Fraraccio, & Dagher, 2003). The release of norepinephrine from the locus coeruleus(Viisanen & Pertovaara, 2010a) and serotonin from the rostroventromedial medulla(Franca et al., 2013; Viisanen & Pertovaara, 2010b) has been assumed to be involved in the analgesic effects of MCS as well. Finally, mechanisms of the descending volleys in the spinal cord have also been described(Franca et al., 2013; Viisanen, Ansah, & Pertovaara, 2012; Viisanen & Pertovaara, 2010b). 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.(Andre-Obadia, Mertens, Gueguen, Peyron, & Garcia-Larrea, 2008; Lefaucheur, Holsheimer, Goujon, Keravel, & Nguyen, 2010; Nguyen, Nizard, Keravel, & Lefaucheur, 2011) 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 (DeFelipe & Farinas, 1992; Jones, 1984; Markram et al., 2004; White, 1989). Next to these neuroanatomical substrates, corollary discharges and the placebo effect 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(Brasil-Neto, 2016). Although several clinical trials showed a significant difference in analgesic effects between sham and active stimulation of the primary motor cortex(Fregni et al., 2006; Lee, Kim, Chun, & Kim, 2012; Velasco et al., 2008), the placebo effect is also hypothesized to play a role in pain relief (Brasil-Neto, 2016; Zubieta & Stohler, 2009).

The release of neurotransmitters can induce a direct effect on the brain, but they can also affect other processes. It has been suggested in animal based studies that electrical stimulation provides a positive effect on the

regeneration of motor axons (axonotmesis)(Nix & Hopf, 1983). Another study shows that part of the neuroplasticity is caused by the release of neurotransmitters. The participation of NMDA (N-meyhyl-D-aspartate) receptors has is thought to play an important role in neuroplastic changes induced by stimulation of the motor cortex(Ambriz-Tututi, Sanchez-Gonzalez, & Drucker-Colin, 2012; Liebetanz, Nitsche, Tergau, & Paulus, 2002).

It is known that every thalamic nucleus receives feedback from the sixth layer of the motor cortex, suggesting that the motor cortex and the thalamus have extensive connections with each other (Sherman, 2016). The fact that these connections and the zona incerta are involved in the regulation of pain, via the GABA-ergic pathways, has been shown extensively(Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2004; Cha, Ji, & Masri, 2013; Lucas, Ji, & Masri, 2011).

Study objective

Is active stimulation still necessary in patients that suffer from chronic orofacial pain who have been successfully treated with MCS for over 4 years or is the analgesic effect caused by permanent axonotmesis?

Study design

Randomized controlled trial

For this study, we aim to include 12 patients that have undergone MCS for treating chronic orofacial pain. All patients have responded favourable to MCS (at least 40% pain reduction) and had at baseline a NRS > 5 (0= no pain, 10= worst possible pain). All patients underwent insertion of electrodes for MCS for chronic neuropathic pain between 2005 and 2012. The investigators (Erkan Kurt and Dylan Henssen) are all part of the medical team that treats or has treated these patients. All patients are contacted by Erkan Kurt in order to inform them about this research. Afterwards, if the patients want to be contacted, they receive an information package, including an information letter and an informed consent form.

All patients are invited to the outpatient clinic to meet with the investigators. After a consultation, the patients meet with the pain nurse (Inge Arnts). She randomizes the patients into two groups in order to create a double-blinded design; blinded for the patients and the investigators. All patients hand over their remote controls of the MCS system. Then, one group (group A) experiences one month without MCS, whereas group B, the other half of the patients, undergo no changes to the MCS system. After one month, all of the patients revisit the outpatient clinic and meet with the pain nurse again. She switches the stimulation conditions between both groups. Again, patients go home for one month. After this month, the patients return to the outpatient

clinic where the pre-existing settings are programmed. The remote controls of the MCS system are then returned to their owners. All the patients meet with the investigator (Dylan Henssen) to talk about their experiences during the last two months. These interviews are audio recorded.
During the two months of the experimental settings, the patients are asked to keep track of their daily quality of life and intake of pain medication (medication type and dosage) by using a personal pain notebook. During the two months at home, patients are allowed to use prescribed pain medication if necessary. Their daily intake must be registered in their daily reports in their notebooks. Also, patients are asked to fill in the McGill Pain Questionnaire once a week.
The aforementioned protocol guarantees a double-blinded, randomized, controlled trial. If patients do experience an uncontrollable increase of pain, patients can always contact the outpatient clinic in order to schedule an appointment with the pain nurse to reprogram their MCS device. After this, the patient will continue the clinical trial. This means that if this request for reprogramming occurs during the first month, the patient will continue the clinical trial in his/her own group (Figure 1).
At the end of the research, the McGill Pain Questionnaires are analyzed using SPSS by the investigator (Dylan Henssen). The audio recorded interviews are transcribed verbatim and analyzed using Atlas.tii. Then, the pain nurse (Inge Arnts) discloses which patient was part of which group.

Study burden and risks

The investigators believe that the pain will not increase during the month in which the electrodes were switched off. We do not believe that patients will experience the pain that they experienced before they were treated. When the pain reoccurs, patients are always invited to the outpatient pain clinic at Dekkerwald-Radboudumc. As always,we take the pain of the patients very serious.

If the pain reoccurs in an unbearable fashion, patients are requested to contact the outpatient pain clinic immediatey. It is always possible to reprogram the settings of the MCS system.

Contacts

Public
Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 2
Nijmegen 6525 EZ
NL
Scientific

Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 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

For this study, we aim to include 12 patients that have undergone MCS for treating chronic orofacial pain. All patients have responded favourable to MCS (at least 40% pain reduction) and had at baseline a NRS > 5 (0= no pain, 10= worst possible pain). All patients underwent insertion of electrodes for MCS for chronic neuropathic pain between 2005 and 2012.

Exclusion criteria

Patients who underwent the insertion of the MCS system after 2012 were excluded. Also, patients that showed an inadequate response to MCS (<40% pain relief) were excluded.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO

Date:	19-09-2017
Application type:	First submission
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	NL61249.091.17