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The role of MRI-guided focused ultrasound in neurosurgery. A narrative review

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ABSTRACT

Introduction. MRgFUS is a novel technology, which can have profound implications in the current treatment of neurological disorders. Its applications range widely, from the alteration of the blood-brain barrier, ablation of tumours to the treatment of movement disorders.

Objective. To review, following thorough research of the literature, the principles of its use in the treatment of neurological diseases and the main reported evidence of its clinical implementation.

Material and method. Interrogation of the MEDLINE database, using the PubMed search engine, for the following MESH words: "MRgFUS", "FUS" "BRAIN", from 2000 to the current year.

Conclusion. MRgFUS can be safely used today for the treatment of Essential Tremor. New research is warranted for the evaluation of its safety and effectiveness in other neurological disorders.

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INTRODUCTION

MRI guided focused ultrasound (MRgFUS) of the brain is a novel technology which has the potential to be implemented successfully in our modern neurosurgical practice. Because of its capability to alter the blood brain barrier, ablate tumors and proven to be effective as a treatment of different movement disorders, it is worthy for us to gain familiarity with this technique. Unfortunately, novelty and the specific technicality of this instrument confuses the clinician. Therefore, we aim in this paper, by the means of a narrative review, to provide an insight on the working mechanism and the uses of the technology and to address the benefits and limitations of its applicability in the clinical practice.

Method

Research of the MEDLINE database, using the PubMed search engine, for the following MESH words: "MRgFUS", "FUS" "BRAIN", from 2000 to the current year.

Background.

First studied by Lynn (1) at the start of the 20th century, the ability to focus ultrasound waves in order to produce a biological effect on the intracranial content was a tempting idea. Aided by the recent advances in high resolution MRI imaging, neuronavigation and the development of hemispheric piezoelectric transducer systems, we are now able to accurately focus the ultrasound waves intracranially, as demonstrated by the commercially available system ExAblate 4000 (InSightec LTD). The result of their application on the tissue can be divided into thermal and mechanical effects. As ultrasounds propagates through the tissue, they raise the local temperature and interact with the gas molecules, producing bubbling, oscillation and finally cavitation with the stretching of the cellular membrane as a result (2) . Based on these mechanical and thermal effects they can reversibly or irreversibly alter the brain tissue, depending on their strength and frequency.

The role of MRgFUS in tumor ablation

Ultrasound can aid in the treatment of deep brain neoplastic lesions, considered unresectable, or in patients that are unfit for surgery. Unfortunately, the data is scarce due to the relative novelty of the technology and the absence of clinical trials (3), (4).

In 2014, Daniel Coluccia published the results regarding the thermoablation of a left thalamic recurrent glioma, using ultrasound. He noticed a 10% reduction in tumoral volume at 5 days post procedure, with improvement in the neurologic status of the patient. At the 21th day check-up no increase in the volume of the tumor was observed (5).

Preliminary results, published by Ernst Martin, creates an insight on the thermoablative tumoral effect of the HIFUS system. Although the author reported clinical improvement in only one patient, it opens the pathway to the development of new clinical trials (6).

The role of MRgFUS on the permeability of the blood-brain barrier

The BBB is a complex structure serving the role of an interface between the blood and the cerebral tissue. Its cytoarchitecture is mainly represented by a layer of endothelial cells, binded one to another by tight junction proteins, interconnected with neurons, perycites and astrocytes (7). This renders it virtually impermeable to exogeneous molecules and thus limiting the effectiveness of different pharmaceuticeuticals. MRgFUS can be used to transiently open the BBB. Hynynen et.al, in his in vivo study, demonstrated that the BBB can safely be opened in rabbits, by applying low strength ultrasounds combined with the intravenous administration of preformed microbubbles. After applying the ultrasound field, these microbubbles oscillate, modify their form, thus stimulating the cerebral blood capillaries and opening the BBB. The effects are transient without significant side-effects (8) (fig 1.). Combining the microbubbles with contrast agent, enables us to accurately pinpoint the target anatomic structure, with the aid of imaging (9).

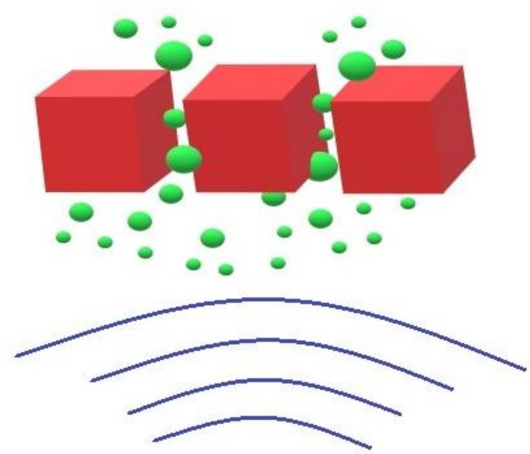

Figure 1. Vascular cells being stimulated (red cubes) by the ultrasound induced cavitation of the microbubbles (green spheres).

Agessandro Abrahao et al, in their human trial of 4 participants suffering from ALS, demonstrated the successful opening of the BBB, after sonification, without side effects (10). MRgFUS can be used in conjunction with systemic chemotherapy in the treatment of intracranial neoplasms. Liu HL et al, in their rat glioma model study, demonstrates a significant survival improvement in the combined treatment group versus the single treatment group (53 days versus 29 days) (11). It appears that the opening of the barrier can significantly enhance the effect of immunotherapy on brain metastases, as demonstrated by Thiele Kobus et al, in their study (12). Finally, it has been shown that MRgFUS cand aid gene therapy pharmaceuticals in their permeation of the BBB as shown by Liu et al in their study (13).

The role of MRgFUS in the treatment of movement disorders and chronic neuropathic pain

Lesioning of the brain by stereotactic techniques along with DBS represent the mainstay of neurosurgical treatment in movement disorders. However, despite their effectiveness, they are not without potential side effects and contraindications. MRgFUS can be a valuable alternative tool in the treatment of these pathologies. Based on the principle of cavitation and thermoablation they can produce discrete lesioning of target anatomical areas, similar with stereotactic radiosurgery, but without harming the surrounding healthy tissue (14). Clearly, a positive ratio of reward versus risk associated with the technique has led different authors to implement it into clinical practice.

Zaaroor et al, in their study investigating the treatment of symptomatic Parkinson Disease and Essential tremor by HIFU VIM thalamotomy, reported a significant improvement in quality of life and reduction of symptomatology by approximatively 50% in the treated subjects. The effects persisted in all but 6 patients, at the 24th month follow-up. Common side effects were transient and represented by gait ataxia, hand paresthesia and asthenia (15).

Martínez-Fernández et al, in their randomised trial investigating the role of HIFU sub-thalamotomy for the treatment of Parkinson Disease numbering 40 subjects, 27 assigned to the procedure group versus 13 to the sham procedure, reported improvement of symptoms at 4 months post procedure by approximatively 50% in the treated subjects vs. the placebo. Common reported side effects are represented by slurred speech, dyskinesia and gait disturbance, with long term persistence in 6 treated patients (16).

Elias et al, in their trial with 76 enrolled participants, investigating the role of HIFU VIM thalamotomy in the treatment of patients suffering from essential tremor refractory to conservative therapy, reported a 41% improvement of the tremor at 3 months post procedure, respectively a 35% percent improvement in the treated group versus the placebo group. Common adverse effects included gait ataxia and paresthesias ,these being present in approximative 36% of the treated subjects (17).

Jin Woo Chang et al, which investigated the use of HIFU VIM thalamotomy in the treatment of refractory essential tremor in 76 patients, reported an overall of 53% improvement of the tremor at one year post procedure. Gait disturbances and paresthesias are reported as the most common adverse effects (18).

Another study investigating the role of HIFU thalamotomy in the treatment of Essential Tremor, with 26 participants, published similar results (19).

The evidence offered by the literature, which proves that HIFU thalamotomy is safe and efficient has led the FDA to approve it, in 2016, for the treatment of Essential Tremor (20), marking a cornerstone in it’s pathway for clinical implementation.

It has been proven that MRgFUS can be used in the treatment of chronic neuropathic pain. First described in 2009, FUS medial thalamotomy can be a viable therapeutic approach of chronic neuropathic pain (21). Marc N Gallay et al, reports improvement of trigeminal neuralgia after central lateral FUS thalamotomy (22). Further clinical trials are needed in order to adequatly asses the possibility of these technique to be safely and successfully used.

Discussion

As previously shown focused ultrasound therapy has the capability to significantly alter the current paradigm of treatment used in neurological diseases. Regarding it’s use on opening the BBB, it is possible that the translation of fundamental science into clinical practice, aided by the future realisation of clinical trials, will usher a new era in Neuro-Oncology (23), (24) and in the treatment of neurodegenerative disorders.

Several studies are currently investigating its role in the treatment of brain ischemia (25), (26). It remains to be seen if it will be effective.

In the field of movement disorders, unfortunately it is now limited only to the treatment of Essential tremor, but probably in the near future, will be extended for Parkinson Disease (27).

New progress in our understanding of the neurological pathology combined with technical improvements will probably advance this technology as a treatment for chronic pain (28) and other neuropsychiatric disorders, such as obsessive-compulsive disorder and depression (29), (30).

Conclusion

MRgFUS is a promising technology in the field of neuroscience. Although currently used in the treatment of movement disorders, further studies are needed for clear identification of its role in the treatment of different neurological diseases.

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