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MRI-Guided Focused Ultrasound, an Emerging Minimally Invasive Technique in Neurology

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ABSTRACT: MRI-guided Low Intensity Focused Ultrasound has a wide range of applications in neurological disorders and is superior to other minimally invasive neuromodulation techniques in terms of a better spatial resolution and stimulating deeper brain structures. Parkinson's disease, Alzheimer's disease, essential tremor, brain malignancy, epilepsy, nerve block, medication delivery, and stroke are among the neurological disorders which benefit from MRI-guided Low-Intensity Focused Ultrasound. In addition, the safety profile of this minimally invasive neurostimulation technique is also well studied and approved. Therefore, the clinical application of Focused Ultrasound in neurologic disorders should be the focus of future clinical trials.

KEYWORDS: Focused, High intensity, Low intensity, MRI-guided, Neurology, Ultrasound

BACKGROUND

Ultrasound describes an acoustic wave of approximately 20 kHz. Besides its diagnostic value as an imaging modality in neurologic disorders, it can also serve as an incisionless neurosurgical procedure for thermoablation, neurostimulation, and modulation of the blood-brain barrier [1]. History of application of Ultrasound back to the nineteenth century began with military applications until lately for diagnostic and treatment purposes [2] with applications in emergency medicine which serves as a valuable tool in the hand of physicians [3].

Examples of some novel diagnostic applications of ultrasonography are the diagnosis of carpal tunnel syndrome during pregnancy with a good acuity [4], Optic nerve ultrasound for early diagnosis of optic neuritis in patients with multiple sclerosis [5], measuring the geometrics of brain structure with clinical importance [6], and Doppler ultrasonography as an alternative diagnostic modality to digital subtraction angiography in detection of extracranial vascular stenosis [7]. The imaging modalities are not always used for their approved application; for instance, MRI could serve to diagnose an uncommon type of bamboo spine which could not be diagnosed by conventional X-ray imaging [8]. Likewise, focused ultrasound was a novel safe procedure introduced for treatment of many clinical conditions, including neurologic disorders.

There are many suggested minimally invasive neurostimulation and Neuromodulation techniques. Among them are Direct Current Stimulation (tDCS) [9], repetitive Magnetic Stimulation (rTMS) [10], and wave-based neuromodulation. For instance, neuromodulation is a novel technique for neuroplasticity with implications for many neurodegenerative and neuroinflammatory disorders [11]. Several mechanisms of action are suggested for Neuromodulation, including electromagnetic field, alteration in gene expression, microglial inhibition, neuroregeneration, and plasticity induction [12].

The safety profile of the application of the Low-Intensity Focused Ultrasound is approved by the food and drug administration (FDA). It is a novel, minimally invasive technique for many neurological disorders [13] [14]. At the same time, this novel therapeutic procedure also was accompanied by some mild neurological adverse effects. Mild to moderate adverse effects by Low Intensity Focused Ultrasound were included neck pain and sleepiness (most common adverse effects), problems with attention, muscle twitches, anxiety, scalp tingling, and transient headache without any life-threatening severe adverse effects, which were similar in severity and profile to the reported adverse effects by other forms of minimally invasive neurostimulation techniques [15]. Most previous studies suggest a good safety profile for Low-Intensity Focused Ultrasound [16]. Sensory side effects of transcortical Low-Intensity Focused Ultrasound depend on the brain region targeted by Ultrasound [17].

A possible suggested mechanism of action of low-Intensity Low-Intensity Focused Ultrasound is its mechanical pressure effect on the cellular membrane ion channels on deep brain nuclei, cortical and peripheral neurons, leading to their stimulation [18]. Improvement of diabetic neuropathy by Low-Intensity Focused Ultrasound is an example of such an effect on peripheral nerves [19].

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Low-Intensity Focused Ultrasound (Low-Intensity Focused Ultrasound), depending on stimulation parameters, can exert a broad spectrum of effects like suppression, stimulation, or tissue ablation. Moreover, Focused Ultrasound has a higher spatial resolution and ability to stimulate deeper brain structures compared to non-invasive electric [20] or magnetic [21] [22] [23] brain stimulation; MRI-guided Low Intensity Focused Ultrasound is a novel neuroprotective minimally-invasive therapeutic approach with implications for a wide range of neurological disorders (e.g., essential tremor, neuropathies, Parkinson associated and essential tremors, brain tumors, etc.) [24] [25].

Focused Ultrasound (LIFU) in Parkinson's disease

Subthalamotomy and thalamotomy by High-Intensity Focused Ultrasound have improved motor signs and reduced tremors in Parkinsonian patients with refraction to medication therapy. However, ipsilateral weakness, ataxia, speech disturbances, and orofacial/finger paresthesia were reported as adverse effects of Low-Intensity Focused Ultrasound [26] [27]. Furthermore, unilateral thalamotomy by High-Intensity Focused Ultrasound improved the quality of life and ability to take care of their activities of daily living in subjects with tremor-dominant Parkinson's disease without cognitive-behavioral and mood adverse effects [28].

Quality of life and psychiatric side effects should be considered when choosing specific treatments for patients with Parkinson's disease [29]. MRI-guided Low Intensity Focused Ultrasound has shown to be non-inferior to DBS in treating tremor signs in parkinsonian patients [30]. In a follow-up of 1 year following administration of Low-Intensity Focused Ultrasound for Parkinson's disease, no serious adverse events were reported. At the same time, there was a significant improvement in tremors and disability of those patients [31]. Focused hand dystonia also improves by induction of MRI-guided Low-Intensity Focused Ultrasound on the ventro-oral nucleus [32]. As a piece of evidence, thalamotomy by Focused Ultrasound also improved multiple sclerosis-related tremors [33] [34].

Focused Ultrasound (LIFU) in essential tremor

The application of High-Intensity Focused Ultrasound in essential tremors for thalamotomy resulted in clinical improvement. The sensory and gait disturbances were the adverse events [35] [36]. Bilateral thalamotomy is as feasible as unilateral Neuromodulation by High-Intensity Focused Ultrasound to improve essential tremors [37]. Low-Intensity Focused Ultrasound for essential tremors improves the severity of tremors and the patients' quality of life besides an outstanding safety profile [38] [39]. Induction of the ventro-intermedius nucleus in patients with non-essential tremors by Low Intensity Focused Ultrasound improves tremors [40].

High Intensity Low Intensity Focused Ultrasound (HIFU) for Alzheimer disease

MRI-guided Low Intensity Focused Ultrasound alters blood-brain barrier permeability [41] with suggested implication in Alzheimer's disease to facilitate medication delivery to the hippocampal region by induction of blood-brain barrier opening at the hippocampal region [42] [43]. An alternative suggested mechanism of its efficacy in Alzheimer's disease is the reduction of the B-amyloid plaques in the hippocampus when it is affected by the focused ultrasound [44]. Another mechanism by which Low Intensity Focused Ultrasound can improve cognitive performance in Alzheimer's is affecting cerebral glucose metabolism [45]. Furthermore, Low Intensity Focused Ultrasound targeting the hippocampus, or the substantia nigra has shown efficacy in treating neurodegenerative dementia by showing at least some improvement in 62.5% of these patients regardless of the treatment they receive. Fine and gross motor performance was also improved in degenerative conditions, and no serious adverse events were observed [46].

High Intensity Low Intensity Focused Ultrasound (HIFU) for medication delivery

MRI-guided Low-Intensity Focused Ultrasound enhanced the delivery of monoclonal antibody Trastuzumab across the blood-brain barrier to Her2-positive breast cancer cells, which have metastasized to the brain [47]. Also, non-Low Intensity Focused Ultrasound combined with microbubble drug delivery has proven effective in enhancing drug delivery to the nervous system [48]. Also, in an experimental setting, low Intensity Focused Ultrasound facilitated the delivery of gene vectors to the brain, suggesting future implications of this emerging technique in clinical trials of central nervous system gene therapy [49]. Patients with Parkinson's disease also benefit from the facilitation of drug delivery to the nervous system by Low-Intensity Focused Ultrasound [50]. Furthermore, low-Intensity Focused Ultrasound improves the trafficking of the immunotherapeutic agents to the brain to facilitate treatment of the brain tumors [51]. Cancer- /chemotherapy-related neuropathy also benefits from low-Intensity Low Intensity Focused Ultrasound with no serious adverse effects [52].

Low Intensity Low Intensity Focused Ultrasound (LIFU) for Ischemic Stroke

Brain stroke is the fifth leading cause of death and a leading cause of disability in the United States. Ischemic central nervous system events affect about a million individuals annually [53]. Low-Intensity Focused Ultrasound has the potential to induce neuronal function in specific regions of the brain. There are pieces of experimental evidence for clinical efficacy from Low-Intensity Focused Ultrasound by inducing neuronal function in ischemic stroke experimental models and decreasing the rate of recurrence and induction of neuronal repair, neuro-angiogenesis, and improvement in neuroplasticity when is administered immediately (less than an hour) following ischemic stroke. In rat models of stroke, it has been shown that Low-Intensity Pulsed Focused Ultrasound induces brain-derived neurotrophic factors and prevents ischemic stroke recurrence [54]. Another experimental study showed restoration of the interhemispheric balance after ischemic stroke by deep cerebellar Low-Intensity Focused Ultrasound [55]. In rat models of stroke, transcranial Low Intensity Focused Ultrasound showed efficacy in decreasing the apparent diffusion coefficient (ADC). Its potency directly depends on the time of treatment from an ischemic event. The sooner the treatment is administered, the more improvement occurs. ADC measures the magnitude of water diffusion in the brain as a parameter in diffusion-weighted imaging (DWI). It is a determinant of the extension of the ischemic lesion and tissue injury [56] [57]. One of the suggested mechanisms by which Focused ultrasound improves recovery after stroke is the induction of angio- neuro- genesis [58]. Low-Intensity Focused Ultrasound in rat models of middle cerebral artery stroke attenuated brain edema, reduced the neuroimmune reactivity at the infarct core and the penumbra, and improved Purkinje cells survival. In addition, it indicates the neuroprotective effect of Low-Intensity Focused Ultrasound [59].

MRI-guided low-Intensity Focused Ultrasound (LIFU) imposed on the brain has shown efficacious effects on improving recovery from stroke. MRI-guided LIFU can be applied in both acute settings and in multiple sessions following AIS to decrease the burden of stroke by improving perfusion to both the main ischemic area and the penumbra, respectively [60]. In experimental studies, Low Intensity Focused Ultrasound has improved thrombolysis by rTPA in carotid artery thrombosis in rats. In addition, low Intensity Focused Ultrasound showed an additive effect on reperfusion by rTPA in carotid thrombosis [61].

Other neurologic disorders

MRI-guided Low Intensity Focused Ultrasound ablates the focus of seizures in the brain. It could be a potential treatment option for epilepsy syndromes [62]. Focused ultrasound can be safely delivered to the focus of the seizure in patients with drug-resistant epilepsy [63]. Affecting the pain circuit, thalamus, anterior cingulate cortex, ventral striatum/internal capsule by focused ultrasound has proven effective in alleviating chronic pain [64]. Nerve conduction block by focused ultrasound could be helpful in the treatment of peripheral sensory disturbances [65].

CONCLUSION

Focused induction of ultrasound on neuronal structures, depending on the parameters of the procedure, can exert stimulation or inhibition of the neurons with implications of focused ultrasound in a wide range of neurologic disorders, including Parkinson's disease, Alzheimer's disease, essential tremor, brain malignancy, epilepsy, nerve block, medication delivery, and stroke. However, the adverse effects from focused ultrasound are very scarce and bearable, with no concerns for serious adverse effects.

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