Focused ultrasound treatment for central nervous system disease: neurosurgeon's perspectives

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Abstract The concept of focused ultrasound (FUS) and its application in the field of medicine have been suggested since the mid-20th century. However, the clinical applications of this technique in central nervous system (CNS) diseases have been extremely limited because the skull inhibits efficient energy transmission. Therefore, early application of FUS treatment was only performed in patients who had already undergone invasive procedures including craniectomy and burr hole trephination. In the 1990s, the phased array technique was developed and this enabled the focus of ultrasonic energy through the skull, and in conjunction with another technique, magnetic resonance thermal monitoring, the possibility of applying FUS in the CNS was further strengthened. The first clinical trial using FUS treatment for CNS diseases was performed in the early 21st century in patients with glioblastoma, which consists of highly malignant primary brain tumors. However, this trial resulted in a failure to make lesions in the tumors. Various causes were suggested for this outcome including different acoustic impedances across heterogeneous intracranial tissue (not only brain tissue, but also fibrous or tumor tissue). To avoid the influence of this factor, the targets for FUS treatment were shifted to functional diseases such as essential tremor, Parkinson's disease, and psychiatric disease, which usually occur in normal brain structures. The first trial for functional diseases was started in 2010, and the results were successful as accurate lesions were made in the target area.

Nowadays, the indication of FUS treatment for functional CNS diseases is gradually widening, and many trials using the FUS technique are reporting good results. In addition to the lesioning technique using high intensity FUS treatment, the possibility of clinical application of low intensity FUS to CNS disease treatment has been investigated at a pre-clinical level, and it is expected that FUS treatment will become one of the most important novel techniques for the treatment of CNS diseases in the near future.

Keywords Central nervous system · Disease · Focus · Ultrasound · Non-invasive

1 Introduction

After the development of modern medical science, treatment efficacy and safety have been major goals in the advances of clinical field. The same applies to the field of neurosurgery, and considering the risk of brain dysfunction after neural injury by neurosurgical treatment, many efforts have been made to find safer therapeutic modalities. In the early 20th century, non- to minimally invasive modalities such as radiation and ultrasound were introduced, and many neurosurgeons tried to adopt these modalities to treat central nervous system (CNS) diseases. For example, the concept of focusing high energy of radiation was applied to the treatment of CNS diseases. This technique was continuously developed and led to modern radiosurgical techniques such as gamma knife radiosurgery [1, 2]. Similarly, the possibility of focusing ultrasound energy for human application was also investigated in the mid-20th century. In 1942, Lynn and Putnam studied the biological effect of high intensity focused ultrasound (FUS) by applying FUS energy to the head and back area of an

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animal such as cat and monkey [3]. Focal lesioning in the brain and spinal cord was observed. However, this experiment was not extended to a human clinical trial because the technique used to control FUS energy was not applicable. Thereafter, few clinical trials on human CNS diseases were performed until the 1990s [4, 5]. Nevertheless, for efficient and safe treatment, all these trials were performed after the removal of the partial skull. Given that one of the important advantages of FUS treatment is its non-invasive nature, at the time, most neurosurgeons did not give attention to the FUS technique performed under invasive craniotomy. However, through the development of the magnetic resonance (MR) technique, the brain could be better visualized, and combined with the phased array technique, the possibility of FUS application in CNS diseases increased substantially in the early 1990s [6–8]. In the mid-1990s, a technique for real time temperature monitoring by MR was developed, which made it possible for FUS treatment to be applied safely [9]. The first human clinical trial using FUS treatment was performed on patients with malignant brain tumors [10]. Three patients with glioblastoma were enrolled onto this trial. Although investigators failed to make lesions in the tumors, they demonstrated that FUS treatment could be applied safely to the human brain. After this trial, many factors for the observed failure were suggested. One of these was the heterogeneity of intracranial tissue among patients with brain tumors. Tumors consisted of many distinct tissues, for example, they might include not only tumor cells, but also neuronal, glial, vessel, and fibrotic tissues. Considering the different acoustic impedances of each tissue, these factors could inhibit the focusing of ultrasonic energy onto the target area. Another possible factor for failure may have been a mechanical limitation; the FUS machine used in this trial had 512 elements, whereas the current machines used for brain application have 1024. Thus, the number of elements in the trial machine was only half that of the current version, and this small number of elements might not apply sufficient energy into the cranium. To overcome the limiting factors described above, machine element numbers were doubled, and the focus of FUS treatments was shifted to CNS diseases involving structurally normal brain tissue.

2 Human clinical trials using FUS

2.1 Neuropathic pain

The first successful application of MR-guided FUS was observed in neuropathic pain treatment [11]. Neuropathic pain is caused by injury of the somatosensory nervous system, and this type of pain is frequently unresponsive to

medical treatment, resulting in a severely disabled life [12]. Jeanmonod et al. performed a clinical trial using MR-guided FUS for patients with chronic neuropathic pain. Twelve patients were enrolled in this trial, and the investigators made a localized thermal lesion at the posterior part of the central lateral thalamic nucleus at peak temperatures between 51 °C and 64 °C. Mean pain relief was 57% at the 1-year follow up, and one patient had a treatment related complication: bleeding with ischemia in the motor thalamus. Although central lateral nucleus thalamotomy is not a commonly used procedure for the treatment of neuropathic pain, this trial was important in that the investigators demonstrated that MR-guided FUS could be used to make relatively safe lesions in the human brain in a non-invasive fashion.

2.2 Essential tremor

Essential tremor (ET) is the most common movement disorder, typically involving a tremor of the arms, hands, or fingers [13]. Medical treatment of ET can ameliorate tremor symptoms for two thirds of patients, while the remaining third manifests with symptoms such as the inability to stop hand shaking and the ability to sing only in vibrato. For these patients, surgical procedures have been applied since the mid-20th century [14]. The most common surgical target for ET is the ventralis intermedius (Vim) nucleus of the thalamus. Thermal or chemical ablation as well as electrical stimulation have previously been used in the attempt to control tremors in patients with ET [15]. Because the anatomical location of the Vim nucleus is relatively close to that of the central point of the human brain, ultrasonic energy transmission into the cranium was expected to be feasible, and ET was considered to be a good candidate disease for MR-guided FUS treatment (Figure 1).

The first trial using MR-guided FUS treatment for ET was started in 2011 at the University of Virginia [16]. Elias et al. conducted an open-label, uncontrolled study of MR-guided unilateral thalamotomy in 15 patients, and the results showed improvement of hand tremor scores from 20.4 at baseline to 5.2 at 12 months after treatment. Four patients enrolled in this trial experienced sensory complications at 12 months after MR-guided FUS treatment. However, no severe complications were observed. The second trial of MR-guided FUS for ET was conducted by Chang et al. [17, 18]. Eleven patients were initially enrolled, and 8 patients completed the study. Similar to the previous trial, all patients who underwent successful Vim nucleus lesioning experienced marked improvements in their tremor symptoms. Interestingly, for 3 patients in this series, the temperature rise at the

Fig. 1 Procedural steps for magnetic resonance guided focused ultrasound treatment

target area failed to rise, and the authors suspected that this could have been attributed to the skull volume in the treatment area.

With the reassurance from the results of this feasibility trial, a multicenter, international, randomized clinical trial was conducted to evaluate the efficacy and safety of MR-guided FUS thalamotomy for essential tremor treatment [19]. A total of 76 patients with medically refractory ET were enrolled, and using a 3:1 ratio, the patients were randomly assigned to undergo either FUS thalamotomy or a sham procedure. According to the results, hand-tremor scores showed a greater improvement after focused ultrasound thalamotomy (from 18.1 points at baseline to 9.6 at 3 months) than after the sham procedure (from 16.0 to 15.8 points); the inter-group difference in mean change was 8.3 points ($p < 0.001$). In the thalamotomy group, adverse events included gait disturbance in 9%, and paresthesia in 14% of patients at 12 months after treatment. Combining the results from several clinical trials of MR-guided FUS thalamotomy for ET, it seems to be true that this technique, which has been shown to have acceptable efficacy and safety levels, could become one of the established treatment options for medically refractory ET [20].

2.3 Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a relatively common psychiatric disorder where people feel the need to check things repeatedly, perform certain routines repeatedly, or have certain thoughts repeatedly [21]. Several neurosurgical procedures including deep brain stimulation and radiofrequency lesioning have been performed for medically refractory cases of this disorder, and the anterior part of the internal capsule of the cerebrum is suggested to be one of the target areas for treatment [22, 23]. Jung et al. tried to make a lesion in the bilateral anterior capsule of patients with medically refractory OCD by MR-guided FUS [24]. Four patients were enrolled in this trial. Outcomes were measured with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), and treatment-related adverse events were evaluated. The results showed improvements in Y-BOCS scores (a mean improvement of 33%) at 6 months after treatment, and no patients experienced adverse events related to the procedures (Figure 2). Despite the small number of patients enrolled, the trial demonstrated that MR-guided FUS treatment could also be applicable to the treatment of psychiatric disorders. Given that many psychiatric disorders share common brain

Fig. 2 Magnetic resonance images after magnetic resonance guided focused ultrasound capsulotomy for obsessive compulsive disorder. Yellow circles indicate focal lesioning of target area

circuits, it is expected that MR-guided FUS might be successfully used in the treatment of other psychiatric disorders such as major depression.

2.4 Brain tumors

After the failure of a clinical trial involving the use of MR-guided FUS ablation in patients with brain tumors, the application of MR-guided FUS for the treatment of brain tumors has been shifting from thermal ablation to modulation of the blood brain barrier (BBB). The BBB is a highly selective permeable barrier that separates circulating blood from the extracellular space of the CNS. In normal conditions, the BBB protects the CNS from toxic materials in the blood. However, it also prevents the penetration of chemotherapeutic agents, which are necessary to control cancer cells in the CNS. Low intensity FUS is known to be able to open the BBB transiently, and several preclinical

studies have also demonstrated the efficacy of a combination of low intensity FUS and chemotherapeutic agent injections for the treatment of malignant brain tumors [25–27] (Figure 3). Although no data regarding the use of FUS for malignant brain tumor treatment by BBB modulation are currently, a feasibility trial for the treatment of metastatic brain tumors from breast cancer using a combination of low intensity FUS and herceptin chemotherapy is currently ongoing [28]. It is expected that if this trial is successful, combination therapy using low intensity FUS and chemotherapy would become one of the treatment options for malignant brain tumors.

2.5 Ongoing preclinical research using FUS for CNS treatment

Besides thermal ablation of CNS tissue, various biological effects of FUS have been investigated. One of these regards

Fig. 3 Low intensity transcranial focused ultrasound sonication for non-invasive opening of blood brain barrier. Blue spot; trans-endothelial leakage of dye (Evans blue) after treatment. No injured vessels were found in treatment area on histological examination

Fig. 4 Trans-endothelial migration of mesenchymal stem cell (MSC) at the site of focused ultrasound sonication. A; site of sonication, B; difference of cell counts (PKH26 immunohistochemistry for mesenchymal stem cell staining, white arrow) between focused ultrasound treated area (ipsilateral, IL), and untreated area (contralateral, CL)

its neuromodulatory effects. There is some evidence for changes in neuronal functions when neurons receive ultrasonic energy. Min et al. observed changes in epileptogenic

activity in rats after FUS treatment, and found that low intensity, pulsed FUS sonication could suppress the number of epileptic signal bursts [29]. Another study by Kim et al.

observed eye movement after low intensity FUS sonication by abducens nerve stimulation [30]. Several postulations have been made regarding the mechanism underlying the neuromodulatory effect of FUS including the hypothesis that FUS might change the permeability of mechano-sensitive calcium channel receptors [31]. It seems to be true that low intensity, pulsed FUS sonication can modulate neuronal function non-invasively. However, further investigation is needed for human application.

Another interesting biological effect of FUS sonication is related to stem cell homing. Many researchers focus on the potential of stem cells for the restoration or protection of neurons. However, there are several limitations to the therapeutic use of stem cells in CNS diseases. Despite the biological capacity and efficacy of stem cells, their implantation in CNS tissue is relatively difficult. Direct injection of stem cells into the brain is the most effective method, but this requires invasive procedures and the target area for transplantation should be limited. Although indirect transplantation via blood vessels was also attempted, the efficacy of transplantation failed to reach therapeutic level. Recently, it was observed that stem cells injected into blood vessels migrated to the area adjacent to an FUS sonication target region [32–34]. This phenomenon was also detected in the CNS. Although further research is necessary, it is anticipated that stem cell application in CNS diseases could be tremendously widened if the transplantation area could be non-invasively modulated by FUS sonication (Figure 4-A, B).

Finally, the application of FUS in the treatment of neurodegenerative diseases, especially Alzheimer's disease (AD) is considered. AD is a chronic neurodegenerative disease that accounts for 60% to 70% of dementia cases. In 2015, there were approximately 48 million people worldwide with AD, and 6–10% of people over 65 years of age were affected by the disease [35]. Treatment for AD is currently very limited, and even with approved medical treatment, it is difficult to reverse the progression of the disease. One of the pathophysiological mechanisms of AD is the accumulation of amyloid plaques, resulting in neuronal loss. Clearance of these amyloid plaques is expected to inhibit further neuronal loss and disease progression. Jordao et al. performed FUS sonication in the cortical area of transgenic AD mice [36]. Interestingly, amyloid plaques within the sonication area were diminished compared to the non-treated area. Behavioral tests also showed some improvement in the FUS treated group. Although this phenomenon should be verified through further investigation, it might be possible to apply FUS treatment to AD patients in the future.

2.6 Unsolved issues

Combining the results from studies using MR guided FUS in the human brain, most patients experienced beneficial

Fig. 5 Tendency of energy requirement during human clinical trials using focused ultrasound thermal ablation according to the skull volume and skull density ratio (SDR). Skulls with higher SDR and lower skull volume in treatment area have tendency to require less maximum energy for thermal ablation although there is no statistical significance due to small number of cases

effects from FUS treatment. However, thermal ablation was unsuccessful for some patients, and several factors have been suggested to explain this. One possible reason could be the differences between individual skulls. The skull is one of the most potent barriers of ultrasonic energy transmission. Although this factor seemed to have been overcome by the use of the phased array technique, the skulls of some patients still do not permit efficient ultrasonic energy transmission. Chang et al. studied the reason for incomplete temperature rise during MR guided FUS ablation by analyzing the results of 25 MR-guided FUS thermal ablations [37]. They found that the skull volume in the treatment area as well as the difference in density between cortical and marrow bone could affect the efficacy of ultrasonic energy transmission (Figure 5). Other skull related factors such as shape, component of marrow bone, and bone health status could also influence energy transmission. Further investigation can be expected to contribute to better selection of patients with skull features that would be appropriate for FUS treatment.

Another possible reason for focusing failure may be the existence of technical/procedural limitations or errors. MR-guided FUS for intracranial application is still at a developing stage. Thus, a procedural technique has not yet been established. However, these factors could be overcome in the near future by advancing treatment algorithms, developing mechanical innovations, and widening the use of MR-guided FUS treatment.

3 Conclusion

Complication avoidance is one of the main issues during the treatment of CNS diseases. Therefore, the development of minimally invasive techniques is critical for minimizing

treatment-related adverse events. In this aspect, FUS application can be an option for safer treatment of CNS diseases. Several clinical trials have validated this hypothesis and many neurosurgeons are trying to widen the application of MR-guided FUS treatment for CNS diseases. Combined with technical advances, it can be expected that MR-guided FUS will play a major role in the treatment of CNS diseases in the near future.

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Compliance with ethical standards

Conflict of interest The authors declares there is no conflict of interest.

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