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Feasibility Study on MR-guided High Intensity Focused Ultrasound Ablation of Sciatic Nerve in a Swine Model - Preliminary Results

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Abstract

Introduction—Spastic patients often seek neurolysis, the permanent destruction of the sciatic nerve, for better pain management. MRI-guided High Intensity Focused Ultrasound (MRgHIFU) may serve as a noninvasive alternative to the prevailing, more intrusive techniques. This *in vivo* acute study is aimed at performing sciatic nerve neurolysis using a clinical MRgHIFU system.

Methods—The HIFU ablation of sciatic nerves was performed in swine (n=5) using a HIFU system integrated with a 3 T MRI scanner. Acute lesions were confirmed using T1-weighted contrast-enhanced (CE) MRI and histopathology using hematoxylin and eosin staining. The animals were euthanized immediately following post-ablation imaging.

Results—Reddening and mild thickening of the nerve and pallor of the adjacent muscle were seen in all animals. The HIFU-treated sections of the nerves displayed nuclear pyknosis of Schwann cells, vascular hyperemia, perineural edema, hyalinization of the collagenous stroma of the nerve, myelin sheet swelling and loss of axons. Ablations were visible on CE MRI. Non-perfused volume of the lesions (5.8 cc – 64.6 cc) linearly correlated with estimated lethal thermal dose volume (4.7 cc – 34.2 cc). Skin burn adjacent to the largest ablated zone was observed in the first animal. Bilateral treatment time ranged from 55–138 minutes, and preparation time required 2 hours on average.

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Ethical Approval: All applicable institutional and/or national guidelines for the care and use of animals were followed.

Conclusion—The acute pilot study in swine demonstrated the feasibility of a noninvasive neurolysis of the sciatic nerve by using a clinical MRgHIFU system. Results revealed that acute HIFU nerve lesions were detectable on CE MRI, gross pathology and histology.

Keywords

HIFU; neurolysis; sciatic nerve; MRI; ablation

Introduction

Patients suffering from spasticity often seek neurolysis, the permanent destruction of the sciatic nerve, in order to improve self-care, balance and global rehabilitation [1–5]. The current methods of neurolysis range from extremely invasive procedures such as neurosurgery [5] to minimally invasive options such as chemical injection [1–4] and thermal ablation [6–8]. However, all these methods are associated with risks of infection, bleeding and damage to other organs [9, 10]. Moreover, the adverse reactions of patients in response to chemical agents can result in chemical neuritis, local fibrosis, neuroma, systemic toxicity and skin damage [11]. In patients with severe coagulopathy, current methods of neurolysis require patient optimization prior to treatment [12].

Magnetic Resonance Imaging guided High Intensity Focused Ultrasound (MRgHIFU) [13, 14] is a unique thermal ablation modality that can noninvasively induce coagulative necrosis of tissues within the body. This ablation modality is used with real-time MRI guidance for both anatomic imaging and temperature monitoring [15]. Continuous monitoring of temperature, a feature that is not available with other image-guidance modalities, provides the feedback necessary for real-time adjustment of ablation and ensures the safety of the procedure. Current clinical applications of MRgHIFU include the ablation of tumors [16–19], functional neurosurgery [20] and palliation of pain in patients with bone metastasis [21]. The lowered risk of complications due to the noninvasive nature of MRgHIFU makes it an attractive modality for neurolysis [22–24].

HIFU has been investigated in *ex vivo* and *in vivo* animal model systems for potential applications in the treatment of spasticity. For instance, the HIFU conduction block in normal and neuropathic sciatic nerves of a rat has been demonstrated *ex vivo* [25]. An *in vivo* study, showing the feasibility of HIFU ablation of sciatic nerve, was performed in a rabbit model using a dedicated short-focal-depth HIFU transducer and ultrasound image guidance [26]. However, studies that utilize the clinical MRgHIFU modality for treatment of the sciatic nerve have not been attempted. Our study is aimed at performing sciatic nerve neurolysis by harnessing the potential of a clinical MRgHIFU system that has already been approved for the treatment of uterine fibroids and painful bone metastasis. The swine model was chosen to approximate human anatomy [23] more closely. Acute lesioning of the nerve was confirmed using T1-weighted contrast-enhanced (CE) MRI and histopathology [27].

Materials and Methods

Porcine In Vivo Study Model

Five Yorkshire swine (Table 1) underwent MRgHIFU ablation of bilateral sciatic nerves. All procedures were carried out according to an approved Institutional Animal Care and Use Committee protocol. Appropriate handling and care was provided by trained staff in accordance with the principles of laboratory animal care and guidelines from the United States Department of Agriculture. Each animal was sedated with Telazol (4.4 mg/kg) and given glycopyrrolate (0.007mg/kg). Animals were anesthetized by intravenous injection of propofol as per protocol. The animals were intubated and a surgical plane of anesthesia was maintained using Isoflurane 2–3% with 100% oxygen on Penlon Nuffield MRI-compatible ventilator. Intravenous infusion of Fentanyl (0.05-0.1 mg/kg/hr) was given for pain management throughout the procedure. Upon completion of ablation procedures and post-ablation imaging, the animals were euthanized, with an overdose via intravenous injection of Euthasol (Pentobarbital Sodium 87 mg/kg and Phenytoin Sodium 11 mg/kg) while under anesthesia.

MRgHIFU Treatment

The animals were treated with a clinical HIFU system (ExAblate 2000®, InSightec Ltd., Tirat Carmel, Israel). After induction of anesthesia, the animals in supine feet-first position were placed on the HIFU table housing a water bath with a HIFU transducer. The ultrasound transducer was operated at central frequency of 1.1 MHz and focal depth of approximately 120 mm, depending on position of sciatic nerve in each animal. To enable the effective acoustic coupling between the skin of the animals and the HIFU transducer bath, a polyacrylamide gel pad was placed and hair was removed from the gluteal region using a razor and hair-removal cream (Nair, Church & Dwight Co., NJ, USA). Both legs of the animal were stabilized by binding them to the table with a non-elastic strap to prevent movement during the experiment. Imaging was performed using 3-Tesla MRI scanner (Signa, GE Healthcare, WI, USA) and a body transmit-receive radio frequency (RF) coil.

For treatment planning, the pelvis and upper thighs of each animal were imaged in three orthogonal planes using T2-weighted, fast spin-echo pulse sequence. After the locations of sciatic nerves were identified by a radiologist as a space between the lateral aspect of ischium and posterior medial aspect of ipsilateral proximal femur, regions of treatment were prescribed on coronal images using planning software. To ensure ablation of the nerve and reliable lesion identification during necropsy, treatment zones covering 4 – 5 cm² area of nerve and adjacent muscle were contoured (Fig 1A). After planning, the accuracy of targeting was verified by applying low-power sonication and by ensuring that the focal locations of planned and actual sonication coincided in coronal and axial planes.

The initial treatment plan, including the target locations, acoustic energy, focal spot size and number of sonications, was prescribed using the treatment planning software and automatically selecting parameters based on uterine fibroid treatment protocol. All treatment target locations were placed at one depth and in a single plane. The prescribed energy and focal spot size were adjusted after the first experiment to avoid excessive muscle necrosis.

Spot size changed, depending on spot type selection and automatically decreased when acoustic energy was set to less than 100% of nominally prescribed energy. For each nerve ablation, the average acoustic energy, percentage of nominally prescribed energy, focal spot size and number of sonications are listed in Table 1. The right sciatic nerve treatment of animal 3 was modified to test a separate hypothesis and was excluded from the analysis in this study. In the first two animals, the treatment of left and right targets was sequential, with left nerve being treated first. In the rest of the animals, the position of sonication was alternated between left and right targets. A cooling time of 90 seconds was allowed to minimize heating in the near field.

To monitor temperature changes during each sonication, a time series of spoiled-gradient echo images was acquired in coronal or axial planes containing the center of a given sonication location. Temperature maps were calculated by planning software from phase difference images according to proton resonance frequency shift (PRFS) baseline-subtraction approach [28] (Fig 1B). For each sonication, InSightec software calculated peak temperature and estimated treated volume as the volume that received the lethal thermal dose (Fig 1C). Percentage of sonications, in which peak temperature reached therapeutic temperature of 55°C was calculated.

Treatment Assessment

The HIFU tissue lesions were assessed using an MRI, followed by histopathology. After ablation was completed, a gadopentetate dimeglumine (Gd) MRI contrast agent (Magnevist, Bayer Healthcare, Bayer), 0.2 mL/kg (0.1 mmol/kg) was injected intravenously, and CE T1-weighted fast spoiled gradient-recalled echo imaging was performed in three orthogonal planes. The post-treatment imaging was not performed in the last animal due to logistical constraints. Presence of a lesion was confirmed by lack of contrast uptake on CE MRI. The size of a lesion was estimated by manual segmentation of the nonperfused volume (NPV). To assess the potential morbidity of the treatment, the skin was visually inspected for signs of burns.

At necropsy, treatment sites were identified through gross visual inspection for regions of red discoloration of the nerve and pallor or adjacent muscle. The sciatic nerve was then removed en bloc with adjacent muscle. Samples of nerves located 5 cm proximally and distally to the treatment site were also obtained. Samples were fixed in 10% neutral buffered formalin for at least 48 hours, and were then sectioned transversely and longitudinally (up to three sections per treatment sites), processed routinely for histology, embedded in paraffin, sectioned at 5 micron thickness, and stained with hematoxylin and eosin (H&E). Upon inspection of histology slides, HIFU ablation of sciatic nerve and adjacent muscle was confirmed on a cellular level.

Statistical Analysis

HIFU parameters, peak temperature and estimated treated volume were recorded for each individual sonication. For every parameter, the average and standard deviation were calculated for each ablation target. InSightec's planning software computed the estimated treated volume by summing the areas of the regions that received lethal thermal dose, and

NPV was calculated by contouring non-enhancing regions on CE MRI images. Linear regression analysis was performed to correlate NPV and estimated treated volume using Excel.

Results

MRgHIFU Treatment

The sciatic nerve was seen on T2-weighted planning images within the space between the lateral aspect of ischium and posterior medial aspect of ipsilateral proximal femur. It appeared as a hypointense tubular structure often surrounded by a fat plane (Fig 1A). Supine positioning of the animals provided an acoustic path to sciatic nerves in all of the animals. Aligning the animal in the center of the treatment window of the InSightec table allowed targeting of both right and left nerves without needing to reposition the animal. Bilateral targeting was achieved by left-right translation of the HIFU transducer inside the HIFU table.

During treatment, the temperature changes were detectable by thermometry imaging (Fig 1B) and, for each treatment, the peak temperature, averaged over the number of sonications, is reported in Table 1. Motion artifacts were visible for several sonications in animal 1 only. In all treatments, the average peak temperature exceeded the therapeutic, 55°C threshold. In 6 treatments, more than 90% of the sonications resulted in peak temperatures greater than 55°C. Thermal dose distribution had either contiguous or spotty appearance (Fig 1C). Tissue volumes between 4.2 cc and 34.2 cc received lethal thermal dose and were qualified as treated by the planning software.

The procedure preparation time including skin preparation, anesthesia, positioning, imaging and euthanasia required 2 ± 0.5 hours on average. Treatment of a unilateral target consisted of 8 to 30 sonications depending on the focal spot size, and the duration of HIFU bilateral ablation treatment ranged from 55 min to 138 min including both sonication and cooling time (Table 1).

Treatment Assessment

On CE T1-weighted MR images, HIFU lesions appeared as centrally hypointense, non-enhancing regions with thin peripheral enhancement (Fig 2). All treatments resulted in lesions visible on CE MRI with NPV measurements reported in Table 1. Out of the seven treatments where contrast-enhanced imaging was performed, six resulted in NPV measuring between 5.8 cc and 18.6 cc. Treatment of the left nerve in animal 1 produced a much larger lesion with NPV of 64.5 cc (Fig 2C). Linear regression analysis showed that the NPV and estimated treated volume linearly correlated with each other ($R = 0.99$) and the NPV-to-estimated-treated-volume ratio ranged from 1.3 to 1.9. Examination of CE images in sagittal and axial planes showed expansion of NPV longitudinally towards femur bone (Fig 2 B-D).

Gross examination of the nerves immediately post-treatment on necropsy showed a well-demarcated segment of reddening and mild thickening of the nerve and pallor of the adjacent muscle (Fig 3) in all animals (Table 1). Upon histological examination (Fig 4A), cellular changes were found in all treated nerves (Table 1). Affected sections of nerve were found

adjacent to affected sections of muscle (Fig 4A), and apparently viable nerve was found adjacent to viable sections of muscle. All HIFU-treated sections of the nerves displayed nuclear pyknosis of Schwann cells, vascular hyperemia, and perineurial edema (Fig 4B). Some specimens also displayed hyalinization of the collagenous stroma of the nerve compatible with intense thermal effect, and numerous clear, empty spaces, compatible with myelin sheet swelling and loss of axons (Fig 4C). Small focal hemorrhages were seen in the adjacent fat plane between the nerve and muscle, and there was edema and necrosis of the adjacent muscle (Fig 4A). For all animals, microscopic analysis showed that the sections of the nerve proximal and distal to the HIFU-treated site were morphologically normal (Fig 4D). Some viable connective tissue was present on the histological sections of both nerve and muscle tissues.

Morbidity

There was one instance of injury to skin tissue. After the treatment of the left sciatic nerve of the first animal, a cutaneous erythema, consistent with HIFU-induced burn, was observed on the skin adjacent to this treatment region.

Discussion

This *in vivo* study demonstrates that a clinical MRgHIFU system, currently in use to ablate uterine fibroids and painful bone metastases, can noninvasively produce acute neurolysis of the sciatic nerve in a swine model. In supine position, bilateral targeting of sciatic nerves was possible without repositioning the animals. The MR-based thermometry allowed temperature monitoring and estimation of treated volume during the treatment. In all treatments in which post-treatment imaging was performed, CE-MRI confirmed ablated tissue lesions, and nerve damage was visible through both gross pathology and histology analysis of all treated animals. Consistent with results from a prior study in a rabbit model [26], our histological analysis showed that HIFU ablation of the sciatic nerve caused structural damage to the nerve fibers and resulted in myelin sheet swelling, loss of axons and nuclear pyknosis of Schwann cells.

While tissue necrosis was achieved in all targeted nerve locations in this study, some viable connective tissue was present on the histological sections of both nerve and muscle tissues. Taking into consideration the inherent latency between the time of acute, non-traumatic nerve injury and the time when light microscopic evidence of damage are first evident [29, 30], future studies may benefit from longer survival times after HIFU treatment, to allow for evolution of nerve injury. In addition, it was previously reported that HIFU could result in the suppression of sciatic nerve conduction *ex vivo* without resulting in observable histological changes [25]. Therefore, combining measurements of evoked potentials [26] with histological analysis will help characterization of treatment outcomes.

To guarantee coverage of the entire nerve and to facilitate identification of the treated nerve region during necropsy, the region of treatment in this study was drawn such that it was larger than the coronal dimensions of the nerve. Furthermore, a focal spot length that was greater than the anticipated diameter of the nerve (10 mm) was chosen. Therefore, muscle necrosis was expected and not considered a negative outcome of the HIFU treatment in this

study. During the very first experiment, notable expansion of ablation towards the skin (Fig. 2C) occurred, resulting in a burn likely due to long focal spot size and near-field heating. Reducing the focal size and acoustic energy in the subsequent experiments (Table 1) mitigated unwanted muscle and skin damage. The observed expansion of NPV towards the bone could be the result of the far-field bone heating, caused by extensive longitudinal dimensions of the focal spot. Due to the high ultrasound absorption coefficient and low heat capacity of the bone, it heats more than the surrounding tissue, and then radiates the heat into the surrounding muscle [31] even after the ultrasound is turned off. For clinical applications, collateral necrosis must be avoided by optimizing the acoustic path to limit the risk of far field bone heating and reflection from the bone. The length of focal spot also needs to be optimized to provide sufficient coverage of the nerve while keeping muscle damage to a minimum. One possible strategy is the use of the shortest focal length while also planning the treatment in more than one plane. Skin burns should be avoided by ensuring good acoustic coupling, sufficient cooling time and by positioning the treatment target at a distance sufficiently away from the skin.

Ideally, HIFU treatment parameters could be further optimized for a range of clinical outcomes including temporary conduction block and permanent axon degeneration and thereby benefit patients with different severities of spasticity and pain. For example, permanent axon degeneration could be a prolonged treatment for spastic patients with complete spinal cord injury. For less severe cases of spasticity and pain, a temporary conduction block could alleviate the symptoms while maintaining some function and muscle strength. Therefore, the effects of the HIFU treatment protocol on nerve conduction and its potential for axon degeneration have to be investigated in the future.

The volume of non-perfused HIFU lesions produced in this study linearly correlated with the estimated, thermal-dose-based treatment volume, thus demonstrating that thermal dose maps can be used to confirm the presence of ablation. However, thermal dose calculations resulted in smaller treated volume estimation than NPV measured on CE MRI. Similarly, in clinical HIFU treatment of uterine fibroids, it was found that thermal dose under-predicted the volume of the treated lesion [31, 32]. In this study, it is possible that the fat surrounding the sciatic nerve could have led to inaccurate MRI thermometry in the voxels with high fraction of lipids, therefore affecting the calculation of the overall thermal dose. To increase the accuracy of treatment volume predictions, an improved calculation of thermal dose [33] would be beneficial.

This study has some limitations, such as small number of animals and inability to carry out post-interventional imaging in one out of the five animals. The effect of HIFU ablation on the nerve conduction was not measured. All animals were euthanized immediately after completion of experiments thus precluding analysis of the long-term effect of HIFU ablation on axon regeneration and nerve conduction. The study was performed in a healthy animal model as only small animal model of spasticity was described to date [34].

In conclusion, the feasibility of a noninvasive neurolysis of sciatic nerve using a clinical MRgHIFU system was demonstrated in this acute study. To further assess the potential of MRgHIFU for neurolysis, longer survival studies and measurements of nerve conduction are

required. These studies in combination with optimization of procedure duration will potentially make MRgHIFU a clinically viable method for treatment of spasticity.

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Figure 1.

A. Cropped coronal T2-weighted planning image (animal 2). Yellow contours are drawn by a radiologist around the left and right sciatic nerves to prescribe the regions of treatment. Yellow dashed box indicates a section, for which thermometry and thermal dose images are shown in B and C. **B.** Single sonication temperature map overlaid on phase-difference image. Pixels with temperature greater than 55 C are shown in red. Red pixels seen away from the prescribed region of treatment are due to imaging artifacts. Circle shows the position of the next planned sonication. **C.** Overlay of the estimated lethal thermal dose distribution at the end of treatment and the T2 planning image (yellow line contours the planned region of treatment). Scale bar: 20 mm.

Figure 2. Post-treatment cropped CE T1-weighted images showing HIFU-ablated tissue as hypointense, non-enhancing regions (arrowheads). Dashed arrows point to the locations of sciatic nerves. Solid arrows point to the expansion of the lesions towards femur bone. **A-B.** Coronal and axial images (animal 2) showing left lesion as the more contiguous, non-enhancing region, compared to the right lesion. **C.** Sagittal image of the largest lesion (animal 1, left side) that resulted in skin burn. **D.** Axial image (animal 4) showing left lesion expanding towards and surrounding the femur bone (the animal was positioned prone during post-treatment imaging). Scale bar: 20 mm.

Figure 3. Gross pathology image of the sciatic nerve and surrounding muscle, post HIFU ablation, shows a full thickness, red discoloration of the sciatic nerve (arrow), corresponding to the HIFU ablation site. The asterisk denotes an adjacent area of muscle pallor from HIFU ablation. Scale bar: 1 cm.

Figure 4.

(A) Low magnification image of the transverse section of the nerve and muscle at the site of ablation. Areas of ablation of the nerve and muscle are delineated. Note vascular hyperemia in the ablated portion of the nerve (arrow), and hemorrhage in the adjacent muscle (asterisk). Scale bar: 1 mm. (B) High magnification, transverse section of the nerve at the site of ablation, (the area within the small box on image A). Note nuclear pyknosis of Schwann cells (arrow), with normal axons and myelin sheaths, and perineurial edema (asterisk) with hyalinization of collagen (arrowhead). Scale bar: 20 μ m. (C) High magnification, transverse section of nerve at site of ablation. Note nuclear pyknosis of Schwann cells (arrow), with dilated myelin sheaths and loss of axons (arrowhead), and perineurial edema (asterisk). Scale bar: 20 μ m. (D) High magnification, transverse section of nerve proximal to site of ablation. All structures are normal. Scale bar: 20 μ m.

Table 1

Summary of treatment parameters and results.

	Animal 1 38 kg		Animal 2 40 kg		Animal 3 19 kg		Animal 4 21 kg		Animal 5 19 kg	
	Right	Left*	Right	Left*	Right	Left	Right	Left	Right	Left
Treatment Parameters										
Acoustic Energy (J)	2120	2176±471	1303	1079±555	-	1314	864	1393	1385	1400
Percentage of Nominal Energy	100%	91±19%	80%	63±23%	-	90%	70%	100%	100%	100%
Number of Sonications	8	19	21	28	-	20	30	24	12	16
Average Spot Length (mm)	27	24.5±4.3	20	14.4±7.8	-	16	12	16	18	18
Average Spot Diameter (mm)	5.6	5.6±1.2	3.8	2.7±1.7	-	4.1	3	4.5	4.5	4.5
Treatment Results										
Average Peak Temperature* (°C)	107±30	86±25	71±26	62±13	-	74±10	64±9	76±10	78±15	71±23
Sonications with T >= 55°C	100%	100%	71%	71%	-	100%	90%	100%	100%	69%
Estimated Treated Volume (cc)	14.1	34.2	4.7	6.8	-	7.5	5.1	11.8	5.5	4.2
Non-Perfused Volume, NPV (cc)	18.6	64.6	8.5	10	-	10.5	5.8	17.8	-	-
Nerve Ablation on Gross Pathology	Y	Y	Y	Y	-	Y	Y	Y	Y	Y
Nerve Ablation on Histology	Y	Y	Y	Y	-	Y	Y	Y	Y	Y
Bilateral Treatment Duration (min)	90		138		41 [†]		88		55	

*Parameters are reported as mean ± standard deviation. Only in animals 1 and 2, left side, treatment plan parameters were varied within the treatment.

[†]Duration of a single nerve treatment.