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17 IN VIVO FEASIBILTIY STUDY OF BOILING HISTOTRIPSY WITH CLINICAL SONALLEVE SYSTEM IN A NEUROLOGICAL PORCINE MODEL

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OBJECTIVES

To determine if a clinical focused ultrasound system (Philips Sonalleve) can be used to perform mechanical liquefaction of brain tissue for neurological lesioning through a simulated fontanelle in a porcine model (simulating neo-natal patients). This work will determine the power of the system required to induce lesions using a boiling histotripsy (BH) pulsing protocol. Post-treatment, the lesion volume and border will be measured with MRI imaging and histological examination.

METHODS

A porcine model was used as the in vivo model with a maximum weight < 6.8 kg (4.9 - 6.8kg). A horse-shoe incision and blunt dissection was used to expose the skull. A craniotomy was performed to create a 4-5 cm^2 opening in the skull simulating the fontanelle in a neonatal patient. A degassed mixture of ultrasound gel and water (ratio 10:1) was poured on top of the dura to ensure good acoustic coupling. The scalp was sutured closed with 2-0 Vicryl cutting needle. The animal was placed supine feet first with the craniotomy centred about the Sonalleve V2 system with Flex-M surface coils. Pre-treatment T1-weighted (T1-w), T2-weighted (T2-w) and T2*-weighted (T2*-w) MRI imaging was conducted as a baseline. Each animal was treated at four cluster locations where each cluster consisted of seven sonication points; one point in the centre and six points uniformly distributed over a 4-mm diameter circle. The clusters were located approximately 15 mm deep in the brain, 7 mm off the midline, and separated by 14 mm in a rectangular geometry. In initial treatment on the first animal, the power was increased from 100 to 500 W for each cluster. After initial analysis, the treatment was repeated on second animal with refined power levels of 325, 350, 375, and 425 W. The treatment sequence consisted of 12000 pulses of 1.2 MHz frequency, 1 and 10 ms pulse duration, and 1% duty cycle for both 1 and 10 ms pulse duration. These protocols have been shown to generate BH lesions in ex vivo bovine liver in another Sonalleve system. During treatment, MR thermometry was used to monitor for surface, focal, and far field heating. A dedicated MATLAB-based interface was connected to the Sonalleve cavitation sensor to detect the signal generated during treatment points. After treatment, post T1-w, T2-w and T2*-w MRI scans were completed for comparison. The animals were euthanized, perfusion fixated and their brains were removed for histology. The brain specimens were cut at the centre for the treatment clusters to get a cross-sectional coronal view where each slice was 5 microns. The slides were stained with haematoxylin and eosin (H&E) and examined for lesion presence, blood and border definition.

RESULTS

A total of 4 piglets were sonicated with the following configuration: 1 piglet with 5 clusters (100 – 500 W), 2 piglets with 4 clusters (325-425W) using 10-ms long pulses and 1 piglet with 4 clusters and 1-ms long pulses. For all power levels, the MR-measured temperature in the near or far field of the treatment was below the noise level. For 10-ms long pulses, 100 and 200 W acoustic powers, no noticeable imaging change was observed during sonication and post-treatment MR evaluation. As power was increased from 300 to 400 W, a temperature increase of up to 5C was measured at the focus. With more discrete power levels, it appeared at 375W that the lesion was more contained whereas higher power levels created wider areas of tissue change. It was observed the timing of MR magnitude of the target cluster changed as the power level increased where the tissue change occurred at 15 s at 300 W, 12 s at 350 W, 10 s at 375 W and 5 s at 425 W. After sonication was completed, the detected temperature rise decreased immediately versus dissipating over time. This would indicate the detected thermometry was due to a phase change of the tissue rather than temperature increase. During treatment, a high amount of lower broad band emissions at frequency < 1.2MHz were detected by a cavitation sensor. Post-treatment MR imaging showed that at power levels between 300 and 400 W, there were areas of hypointensity indicating the lesion. H&E staining confirmed the presence of the mechanical lesion where various anatomical targets were fractionated. Power levels were sufficient to rupture vessels and cause a focused area of haemorrhage at the treatment cluster. It showed that BH treatment dissolved the anterior ventricle wall with presence of elements of blood. H&E staining also showed that maximum lesion diameter was approximate 7 mm in coronal plane therefore the treatment borders matched the treatment plan. For the piglet treated with 1-ms long pulses, the post-treatment imaging change was not noticeable. However, at 375 and 400 W power, H&E slides showed two areas where there was a perforation of the anterior ventricle wall with a lesion size of up to 2 mm. It appeared that the shorter pulse duration generated smaller but more focused lesions.

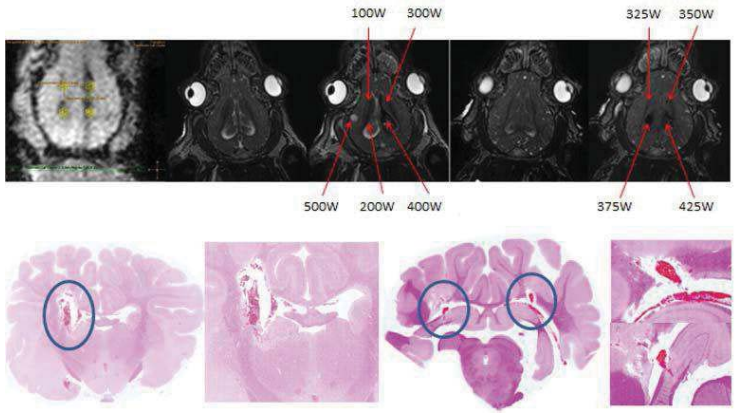

Figure 1: Top Row: Left to Right: Treatment area, Pre T2-w (100-500 W), Post T2-w (100-500 W), Pre- T2-w (325-425) and Post T2-w (325-425); Bottom Row: Histology Left to Right: 10 ms treatment (375W), 10 ms treatment - zoomed (375W), 1ms treatment (375W and 425W), 1 ms treatment – zoomed.

CONCLUSIONS

This pilot study shows that the clinical Sonalleve system is capable of generating mechanical ablation of a brain tissue in an in vivo porcine model using boiling histotripsy pulsing scheme. The power threshold to initiate lesions in brain using 10 ms pulses (375 W) was found to be similar the power levels used in BH studies in ex vivo bovine liver and porcine kidney tissue at a similar depth in tissue (250 – 300 W) in a Sonalleve V2 system at the University of Washington. The treatments can be accelerated by using higher power outputs and shorter pulses. H&E histological evaluation showed that BH treatment caused rupture of vessels focally while also creating wider well defined areas of mechanical ablation with no damage to surrounding tissue. Additional work is underway to characterize the pressure levels generated by the Sonalleve to correlate the power and pressure for treatment.