10/17/10

Final Progress Report for FUSF Research Award:

Feasibility of ablating brain regions adjacent to the optic nerve while retaining nerve function with focused ultrasound combined with an ultrasound contrast agent

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Background/Introduction: This study investigated the feasibility of using focused ultrasound (FUS) to ablate a targeted region adjacent to the optic nerve without causing damage to the nerve itself. We investigated sonication combined with an US contrast agent (Definity), with a hypothesis that it can (1) achieve ablation at reduced exposure levels that avoid bone heating and (2) result in little direct damage to the nerve itself due to its relative paucity of blood vessels.

Methods: Burst sonications (PRF 1 Hz; duty cycle 1%; duration 5 min) were performed in a 4.7T MRI using a 525 kHz transducer (diameter/ROC: 4/3 cm). Lesions were created transcranially in the brains of 22 Sprague Dawley rats. The focal region was targeted on or directly adjacent to the optic nerve, optic tract or optic chiasma. Three exposure levels were tested (0.8, 1, and 1.25 W). Prior to each sonication, Definity (Lantheus Medical Imaging, Inc, MA, USA) of 10µl/kg (10 animals) or 20µl/kg (12 animals) was administered intravenously. Optic nerve damage was monitored by recording visual evoked potentials (VEP) using MRI-compatible electrodes (IVES EEG solutions Inc., Manotick, Ontario, Canada) implanted epidurally into the occipital cortex. Contrast enhanced T1 weighted, T2-weighted and T2*-weighted MR images were used to evaluate the resulting lesions in MRI. Animals were euthanized after 24, 48, 72 hrs, 8 days, or 2 or 3 weeks and brains were removed for histopathological evaluation.

Results & Conclusions: FUS exposure at 0.8 W with 20µl/kg Definity resulted in infracted regions. All cellular elements appeared necrotic, and macrophages infiltration was evident. Three weeks after sonication, the necrotic brain tissue at the targeted location disappeared, and a cyst was evident along with enlarged brain ventricles. Sonication at 1W with 10µ/kg Definity produced smaller size lesion areas. MRI suggested hemorrhagic lesions surrounded by edema and BBB disruption. Despite the fact that the lesions were targeted on or within 1 mm of the optic nerve, tract, or chiasma, visual function as measured by VEP recording did not appear to be severely affected. There was no significant ($P>0.05$) reduction in the amplitudes of the early VEP components (P1-N1 and N1-P2) compared with pre-sonication tests. Although some animals showed slight changes in the amplitude of VEP components, these differences were not significant in 20/22 animals. The latencies of VEP components (P1, N1, and P2) were unaffected or slightly changed; however, the changes were not significant. In conclusion, this preliminary functional and histopathological data suggest that pulsed sonication combined with an ultrasound contrast agent can be used to ablate tissue directly adjacent to the optic nerve while preserving major nerve function. Future work is necessary to evaluate whether more subtle nerve damage results from such exposures.

Acknowledgements (Funding): Supported by a grant from the Focused Ultrasound Surgery Foundation and NIH grant R01EB003268.