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Histotripsy: potential non-invasive management of Intracerebral Hemorrhage

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ICH affects nearly 1.9 million people world-wide with a 25–40% one-month mortality[1]. Primary ICH leads to rise in intracranial pressure (ICP) thus creating for a hypoperfusion state. In addition, the degradation of red blood cells leads to formation of oxidating agents which lead to cellular injury as well as creating for a pro-inflammatory state[2]. The removal of ICH has the theoretical ability to reduce ICP as well as to remove the substrate leading to neurotoxin formation. In the most recent MISTIE III trial, the authors reported that the patients with greatest amount of hematoma evacuated had better clinical outcomes[3]. Current paradigms of tPA + ventricular drain, endoscopic techniques, and SCUBA technique each have their strengths and weaknesses, necessitating a technology which allows for a noninvasive technique with drainage via the commonly performed ventriculostomy procedure[4, 5]. Histotripsy uses high-pressure microsecond-length ultrasound pulses applied from outside the skull and focus to a volume measuring 1–2 mm in diameter, leading to the formation of a cloud of cavitation microbubbles. The high local stress and strain induced by the rapid growth and collapse of the microbubbles lead to liquefaction of the treated substance into acellular debris. Histotripsy has been investigated to noninvasively liquefy the ICH within minutes. Given the potential therapeutic benefit of ICH evacuation, we report the first series of results of utilizing the non-invasive technique of histotripsy to liquefy ICH thus allowing for ventriculostomy based drainage.

With in-vitro analyses, we aimed to understand the ability of the histotripsy array to liquefy in-vitro clot as well as to evaluate optimal settings. A 256 element - 500 KHz, hemispheric array was utilized to treat in-vitro spherical clot samples measuring 33.5 ml (4 cm diameter clot)[6]. Treatment was carried out through 3 skull caps to mimic transcranial treatment as well as to determine rise in skull temperatures. At the fastest rate we were able to liquefy in-vitro clot at 16.6 ml/minute with the temperature rise within the skull at less than 4°C[6]. The variation of the skull thickness and the significantly higher speed of sound in the skull compared to the soft tissue causes reduced focal pressure and distorts the focal volume for ultrasound traveling through skull. Thus we have developed a ventriculostomy catheter with acoustic hydrophone at the tip which allows for aberration correction and increase in focal

pressure at the geometric focus by nearly 60%[7]. In a future state, the placement of a hydrophone coated ventriculostomy catheter will allow for more efficient treatment of ICH as well as to allow drainage of the clot in real time.

With optimization of the histotripsy apparatus through in-vitro studies, we moved towards in-vivo studies by first performing an in vivo safety study in the normal swine brain. Our goal initially was to create histotripsy lesion within the swine brain to evaluate feasibility as well as safety. Unlike human skull, swine skull is flat and thick, thus unamenable for ultrasound propagation. Thus, we created a small craniectomy of the swine skull and then performed the histotripsy treatments through a transdural approach. Histotripsy was utilized to create swine brain lesions measuring up to 1cm in dimeter. The animals were survived for 72 hours and then sacrificed for MRI and histological evaluation[8, 9]. Post histotripsy treatment there were no changes in clinical functionality. The MRI and histological evaluation at 72 hours revealed no evidence of significant edema, hemorrhage, or inflammation. In addition, we were able to create lesions with no sign of injury within 100 um of the target[8].

We then moved towards treating a well-accepted swine ICH model with histotripsy to evaluate safety and efficacy. We formed 1.75 cc clots within the frontal lobe of the swine utilizing autologous blood delivered with a pressurized pump and then allowed for the swine to recover for 48 hours. A craniectomy was then performed and the center of the clot was treated with histotripsy with some animals undergoing evacuation while others did not have drainage. Swine were sacrificed at 6 hours post histotripsy treatment as well as at 7–8 days post ICH formation. We were able to successfully target the center of the clot with evacuation of nearly 1cc post treatment[8]. There was minimal perihematomal injury. There were no neurological deficits within the swine nor were there signs of neurological dysfunction.

The above studies have allowed us to demonstrate the feasibility and safety of using histotripsy for treatment of ICH in a swine model. Current and future studies will involve transcranial histotripsy of swine ICH model with long-term survival as well as treatment of cadaveric specimens deceased from primary ICH. Histotripsy is a non-invasive technique with future promise for liquefying large volumes of ICH in minutes and thus allowing for drainage via a ventriculostomy catheter.

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