Non-Invasive Diagnosis of Intracerebral Hemorrhage Using Iodinated Liposomal Nanocarriers

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Statement of Purpose: Head injuries often result in intracranial hemorrhage (ICH) most commonly diagnosed through CT imaging[1]. Some intracranial injuries are difficult to detect with CT and require contrast enhancement or MRI[1,2]. Currently used CT contrast agents undergo rapid renal clearance and are unsafe for patients with reduced kidney function[3]. MRI is less useful in the emergency setting due to lengthy acquisition times, inaccessibility of equipment, and incompatibility with metallic foreign bodies, implants, and instruments used in emergency care[4]. Improvement in diagnostic identification of ICH would be advantageous particularly if the detection accuracy could be improved utilizing a single, rapid imaging modality.

Liposomal nanocarriers can be utilized as delivery vehicles for contrast agents to enable rapid non-invasive imaging of the blood pool[5] and compromised vasculature[6]. Liposomes increase the circulation time of encapsulated contrast agents and are cleared by the liver thereby avoiding potential renal toxicities[7]. The relatively large size (100nm) of liposomes enables them to discriminate between intact and compromised vasculature which makes them suitable carriers for CT contrast agents utilized for detection of ICH following traumatic injury.

Methods: ICH was induced in rats through a 10 minute intracerebral infusion of 1 ul bacterial collagenase (1 CDU) 3mm lateral of bregma at a depth of 3mm. Rats were imaged using CT after intravenous administration of free or liposomal iodine based contrast agent delivered approximately 1 hour after induction of ICH.

Results: ICH is apparent in the brain of a rat 1 hour after intracerebral administration of collagenase into the left hemisphere (Figure 1). Histological analysis verified the influx of red blood cells into surrounding brain tissue. Using CT imaging, ICH could not be seen in rats treated with free contrast agent but was clearly identified in the left hemisphere of rats treated with liposomal contrast agent (Figure 2).

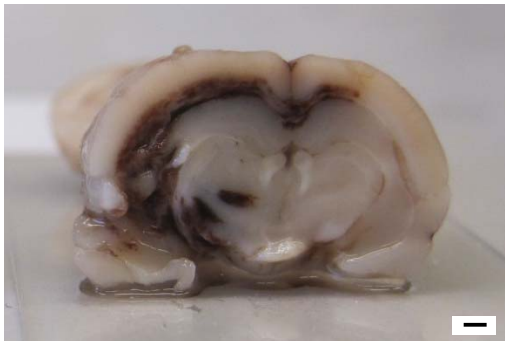

Figure 1. Transverse view of rat brain 1.5 hours after intercerebal administration of collagenase into the left hemisphere. Scale bar is 1mm.

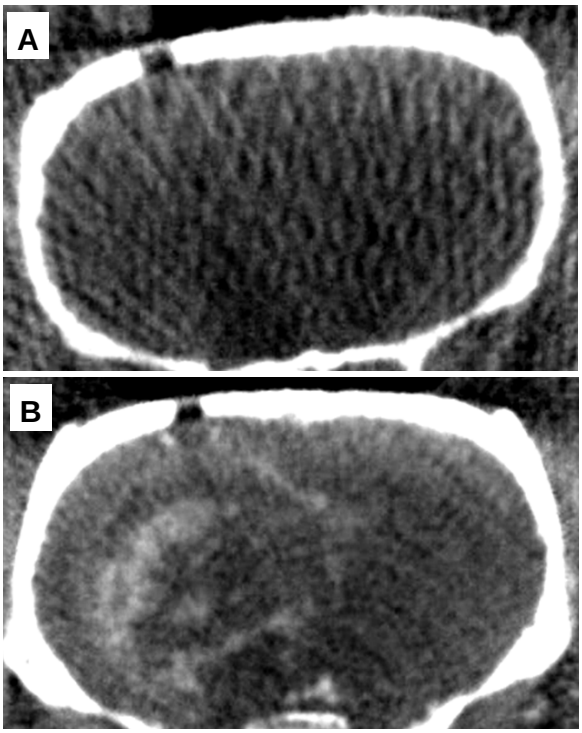

Figure 2. MicroCT images of ICH rat brains. Axial view of injured rat brains after intravenous administration of free (A) or liposomal (B) CT contrast agent. Images were acquired 2 hours after intracerebral administration of collagenase into the left hemisphere. Enhanced contrast is apparent at the injury site directly below the burr hole in the skull for animals receiving liposomal contrast agent; whereas administration of free contrast agent did not result in contrast enhancement.

Conclusions: We have developed a novel nanocarrier encapsulated contrast agent which enables rapid, non-invasive imaging of ICH. This agent is able to discriminate between intact and compromised vasculature since its size restricts extravasation across intact blood vessels. ICH can be detected rapidly and non-invasively utilizing this agent in combination with CT imaging. This agent does not undergo renal clearance making it safe for patients with compromised kidney function.

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