The sub-chronic vascular response to water-borne embolic coacervates.

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Introduction: In a transcatheter embolization procedure, an embolic agent is delivered locally via a microcatheter to obstruct blood flow in a blood vessel or vascular bed. Liquid embolic agents are used in small vessel embolization and have a low viscosity injectable form, allowing their delivery through long narrow microcatheters and transition into a more solid form in the blood vessel1. Current clinically available liquid embolic agents include alkyl cyanoacrylates which polymerize upon contact with blood and water-insoluble copolymers (most commonly ethylene vinyl alcohol) dissolved in water-miscible DMSO which precipitate inside the vessel. Cyanoacrylate based embolic agents contain reactive, rapidly-polymerizing components, making them difficult to control and causing adverse tissue reactions2. DMSO used in precipitating systems is toxic and can cause pain, vasospasm, and angionecrosis3, 4. In order to overcome these toxicity and handling problems, water-borne, embolic coacervates were developed that solidify in situ in response to decreasing ionic strength. Complete arterial devascularization was achieved during transcatheter embolization of a rabbit kidney5. Longer-term tissue response was evaluated in a rabbit auricular artery model.

Materials and Methods: Coacervates were produced by mixing solutions of the oppositely charged polyelectrolytes protamine sulfate (PRT) and sodium hexametaphosphate (P6) at a 1:1 charge ratio. Tantalum oxide powder (TaO) was added as a contrast agent. The resulting mixture produced a distinct liquid-liquid phase separation, and the polymer-rich dense phase was used as the in-situ solidifying embolic agent. The sub-chronic vascular response was evaluated by injecting the material into the central auricular artery of a rabbit using an intravascular catheter. Tissue was harvested at 0, 14, and 28 days (1 animal per time point). Sections were paraffin embedded, sectioned to 5 μm, and stained with Hematoxylin & Eosin. Sections were evaluated for signs of vascular occlusion, vessel wall integrity, angionecrosis, and fibrosis.

Results and Discussion: Histological examination showed complete occlusion of arteries injected with the embolic coacervates. Vascular endothelium and elastic media remained intact throughout the embolized vessels, even when in direct contact with the coacervates, and there were no signs of angionecrosis, which is widespread with other liquid embolic agents. Like these other agents, occlusion is dependent upon both mechanical obstruction of the vessel with the embolic material and native thrombus resulting from blood interactions with the material (Fig. 1). In acute time points, this thrombus is unorganized with signs of inflammation. Over time, the thrombus becomes more organized with the ingrowth of fibroblasts and onset of fibrosis, which is most evident at 28 days (Fig. 1). The continuation of the processes at 28 days will likely result in fibrous encapsulation of the embolic material, anchoring it to the tissue, sequestering its contents, and stabilizing the occlusion.

Conclusions: Embolic coacervates demonstrated a benign foreign body response, which supported tissue ingrowth and stabilized vessel occlusion out to 28 days. While embolic coacervates remain a promising agent for capillary level embolization applications, longer studies (out to 6 months) are needed with larger numbers of animals to better assess the potential for recanalization, low incidence complications, and long-term risks.