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Commentary

Acoustically Activated Nanodroplets for Simultaneous Imaging and Thrombolysis of Acute Ischemic Stroke

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DESCRIPTION

Acute ischemic stroke requires rapid intervention to restore cerebral blood flow, with time to recanalization directly influencing patient outcomes. Current approaches include intravenous thrombolytics, which often achieve incomplete recanalization, and mechanical thrombectomy, which requires specialized facilities and personnel. We have developed acoustically activated nanodroplets capable of both ultrasound-guided imaging and targeted thrombolysis, potentially enabling earlier and more effective intervention in the critical time window following stroke onset. These perfluorocarbon nanodroplets, approximately 250nm in diameter, encapsulate recombinant tissue Plasminogen Activator (rtPA) within a stabilizing phospholipid shell that can be triggered to release the thrombolytic payload and simultaneously enhance ultrasound imaging contrast through controlled vaporization.

The nanodroplets were synthesized through a microfluidic emulsification process utilizing a perfluoropentane core surrounded by a lipid monolayer incorporating polyethylene glycol chains for stabilization and fibrin-targeting peptides for thrombus-specific accumulation. The rtPA was conjugated to the inner surface of the lipid shell through a thermolabile linker, enabling release during phase transition while protecting the enzyme from inhibitors in circulation. This architecture creates a stable nanoemulsion at physiological temperature that can be activated by focused ultrasound to undergo a liquid-to-gas phase transition, simultaneously releasing the thrombolytic payload and generating microbubbles that enhance ultrasound contrast at the target site.

In vitro characterization using human blood clots demonstrated enhanced fibrinolytic activity compared to free rtPA, with approximately 3.2-fold acceleration of clot dissolution under ultrasound exposure. The targeting peptides facilitated accumulation within the fibrin mesh, achieving local rtPA concentrations approximately 7-fold higher than surrounding medium as confirmed by fluorescence microscopy. Importantly, the encapsulation protected rtPA from major inhibitors including Plasminogen Activator Inhibitor-1 (PAI-1) and α2-antiplasmin, extending its functional half-life from approximately 5 minutes to over 45 minutes in human plasma. Contrast-enhanced ultrasound imaging confirmed excellent visualization capabilities, with enhancement ratios exceeding 25dB following activation.

In vivo evaluation utilized a thromboembolic stroke model in rats, with the middle cerebral artery occluded using autologous blood clots. Administration of the nanodroplets followed by transcranial ultrasound application (administered 60 minutes post-occlusion) resulted in successful recanalization in 82% of animals compared to 43% with standard rtPA treatment at equivalent doses. Magnetic resonance imaging demonstrated significant reduction in infarct volumes (approximately 58% smaller compared to control groups) and improved cerebral blood flow in previously ischemic territories. Notably, the nanodroplet formulation achieved these improvements while using approximately 70% less total rtPA, potentially reducing hemorrhagic transformation risk a major complication of thrombolytic therapy.

CONCLUSION

Safety evaluation revealed no evidence of intracerebral hemorrhage at effective doses, with histopathological examination confirming intact cerebral vasculature and blood-brain barrier integrity as assessed by Evans blue extravasation. Hematological parameters remained within normal ranges, with no significant alterations in coagulation factors or platelet function observed. The perfluorocarbon component demonstrated expected clearance through pulmonary exhalation, with no evidence of tissue accumulation beyond 24 hours post-administration. These acoustically activated nanodroplets represent a promising approach for combined diagnostic and therapeutic management of acute ischemic stroke, potentially extending the treatment window while improving efficacy and safety profiles compared to conventional thrombolysis. Our results indicate that Acoustically Activated Nanodroplets (AANs) not only improve therapeutic precision

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but also reduce systemic exposure to thrombolytic agents, potentially minimizing associated hemorrhagic risks. As such, AANs represent a significant advancement in stroke theranostics, paving the way for integrated diagnostic and therapeutic strategies in cerebrovascular disease management.