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Aptamer Inhibition of Von Willebrand Factor Provides Thrombolytic Efficacy and Decreased Stroke Burden without an Increased Risk of Intracranial Hemorrhage

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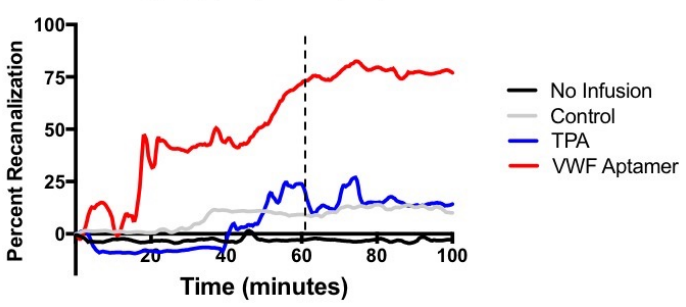
Introduction

Stroke remains a major cause of morbidity and mortality, and with numerous trials revealing the efficacy of mechanical thrombectomy, it has become a prominent neurosurgical entity. While recombinant tissue plasminogen activator (rTPA) has been the mainstay of ischemic stroke treatment, few patients are eligible for treatment, and recanalization is only seen in 25-50%.

Aptamers are a class of RNA molecules that bind and inhibit proteins. An aptamer binding von Willebrand factor (VWF) and inhibiting its interaction with glycoprotein Ib-IX-V was recently developed, preventing platelet adhesion and aggregation. Previous work with the VWF aptamer has demonstrated efficacy in thrombolysis (Figure 1).

Figure 1



VWF aptamer promotes more significant and prolonged thrombolysis than rTPA or controls

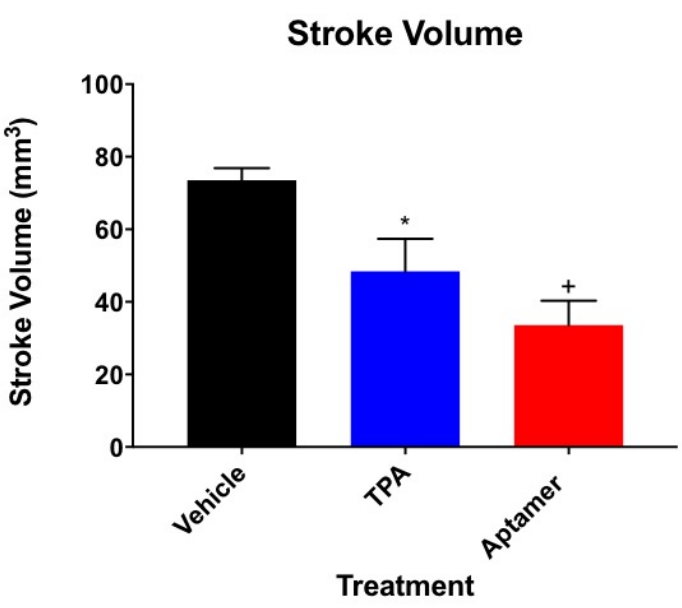
Results

Stroke volume was significantly decreased in mice treated with VWF aptamer (33.57 ± 6.743 mm3, +p<0.0001) and rTPA (48.4 ± 9.00 mm3, *p<0.01) compared to vehicle (73.54 ± 3.31 mm3)(Figure 2). ICH volumes in mice treated with rTPA (1.88 ± 0.51 mm3) were significantly (^p<0.05) higher than both vehicle (1.04 ± 0.10 mm3) and VWF aptamer (0.94 ± 0.11 mm3)(Figure 3).

Methods

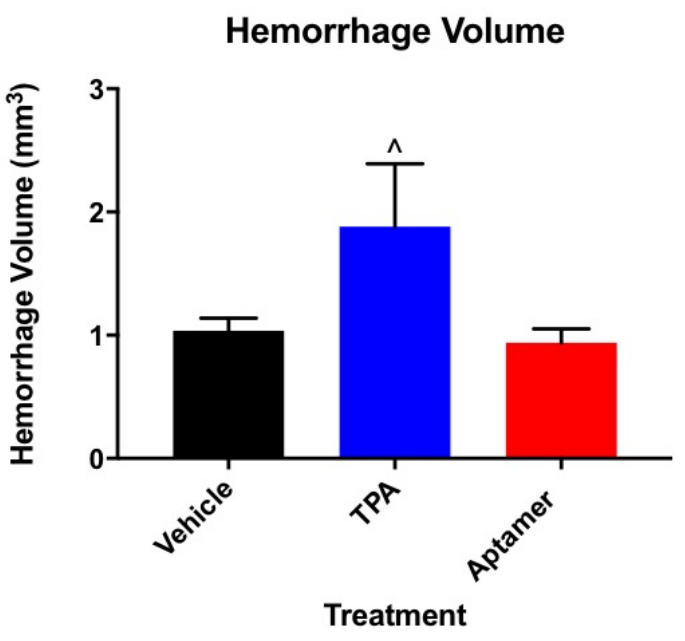
Adult wild-type (C57BL/6J) mice were anesthetized, and the right carotid artery was exposed. A 6-0 nylon suture was advanced within the internal carotid artery to generate vascular injury and intracranial hemorrhage (ICH). Vehicle (platelet binding buffer, n=17), rTPA (n=10) or VWF aptamer (n=14) was then administered. An MRI was obtained after 90 minutes to assess stroke and ICH volumes.

Figure 2



VWF aptamer decreases stroke burden

Figure 3



VWF aptamer does not increase ICH

Conclusions

Aptamer inhibition of VWF is a potent thrombolytic agent with greater efficacy than rTPA. VWF aptamer also significantly decreases stroke burden compared to control. Furthermore, this aptamer carrys no increased risk of intracranial hemorrhage, an advantage this agent provides over rTPA and current intravenous anti-platelet therapies. This provides a novel therapeutic strategy for thrombotic occlusion in the stroke population with greater efficacy than current standards of care and an improved safety profile.