ACTIN IMPARTS THROMBOLYSIS RESISTANCE IN ACUTE ISCHEMIC STROKE CLOTS – GELSOIN ACCELERATES TPA MEDIATED THROMBOLYSIS


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Introduction

Tissue-type plasminogen activator (tPA) is the only FDA approved thrombolytic agent used for acute ischemic stroke treatment (AIS). However, the recanalization after tPA is achieved only in 50% of patients. Recent evidence showed that most embolic clots retrieved from large vessel occlusion (LVO)-stroke patients are composed of a thick outer coating of NETs, platelets, and vWF, which could be responsible for thrombolysis resistance. The purpose of this study was to assess the role of actin, cytoskeletal protein, in clot’s resistance to tPA. We hypothesize that the combination of actinolysis and fibrinolysis will have better prothrombolytic activity than fibrinolysis alone.

Materials and Methods

Thrombectomy retrieved clots (n=26) were obtained from stroke patients as part of the STRIP (Stroke Thromboembolism Registry of Imaging and Pathology) study. Martius Scarlet Blue staining and immunostaining for actin were performed on the clot sections to correlate the level of actin with other major clot components. Red blood cell-rich, fibrin-rich, and platelet-rich clot analogs were made in vitro. Ex vivo thrombolysis assay using tPA was performed in clot analogs, and fresh AIS clots received from patients with or without gelsolin, an actin severing molecule.

Results

Thrombectomy retrieved stroke patient clots had a higher proportion of actin (Mean=72.98±3.88), with a significant positive correlation with platelets (p<0.05) and a significant negative correlation with RBC content (p<0.05). Immunohistochemistry confirmed the presence of actin in the clot mimics. Both clot analogs and patient thrombi from patients showed 20–40% more thrombolysis with gelsolin and tPA combination compared to tPA alone. The confocal microscopic images confirmed fibrin fragmentation after actinolysis and thrombolysis in the clots.

Conclusion

Actin is one of the major structural components of AIS clots and could be responsible for fibrinolytic resistance. Targeting actin molecules would positively impact improving the outcome of recanalization of LVO-AIS.