Intra-arterial pharmacotherapy administration following experimental stroke improves neuronal survival and functional outcome.

Michael Maniskas, PhD[1] • Jill Roberts, PhD[2] • Gregory Bix, MD, PhD 3 • Justin Fraser, MD[1]

[1]Neurosurgery, University of Kentucky • [2]Sanders Brown Center on Aging, University of Kentucky • [3]Neurology, University of Kentucky

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The disconnect between laboratory stroke models and the human clinical condition has long been recognized as a limitation to translating preclinical neuroprotective research into therapeutics.

Experimental neuroprotective stroke therapies may fail, in part, due to their inability to reach stroke- affected brain tissue if the blood clot has not been removed prior to treatment. To that end, we proposed to use the MCAo mouse stroke model in combination with post-reperfusion selective intra-arterial (IA) neuroprotectant administration to accurately mimic large vessel occlusion and the IA techniques used during surgical thrombectomy in patients, respectively. Given the complex pathways involved in stroke, it is also unlikely that monotherapy would yield highly significant benefits in the human condition. Therefore, we proposed to study synergistic effects of two neuroprotective agents administered selectively after stroke reperfusion.

We administered two distinct neuroprotective agents, a calcium channel blocker and an experimental NMDA receptor modulator. Selective administration of either agent significantly reduced mean brain infarct volumes and improved functional outcomes without any systemic side- effects. Selective IA administration of these agents following successful recanalization proved safe under physiological measurements of heart rate and blood pressure when compared to IA control (saline). We next looked at blood flow through the MCA following drug administration and found no difference between IA administration of combinational therapy and IA control. To determine the potential effects of IA therapy on post-stroke motor function, we exposed the mice to both rotor rod and open field motor assessment at baseline (before stroke), post-stroke day (PSD) 1 and 7. We noted a significant increase in functional recovery from PSD 1 to PSD 7 in both tests. Lastly we examined infarct volume and found a significant reduction (75%) when comparing IA combination versus IA control. We conclude that the selective IA administration of potential neuroprotective agents can be successfully modeled in the laboratory to mimic contemporary human large vessel acute stroke management and may result in the successful translation of experimental stroke treatments.