

## Introduction

As thrombectomy is now a standard of care for emergent large vessel occlusion (ELVO), there is a new opportunity to explore potential adjunctive neuroprotective compounds that can be administered following recanalization. Verapamil has a well-documented history of being used as a vasodilator intracranially, but recent data suggests a neuroprotective effect as well.

## Methods

We evaluated the efficacy of verapamil administration through two models of stroke in conjunction with a Phase I clinical trial; in vitro oxygen glucose deprivation (OGD), in vivo tandem transient middle cerebral/common carotid artery occlusion (MCAo) with intra-arterial (IA) injection, and a Phase I clinical trial to determine safety.

## Results

Starting in vitro, with OGD studies we exposed mouse brain endothelial cells and neuronal cell lines to OGD conditions followed by 15 minute reperfusion with verapamil treatment followed by 24 hour reperfusion. Results from cell viability assays showed a significant increase in cellular activity for those cells treated with verapamil when compared to control (Figure 1). Second, in vivo studies of C57/Bl6 male mice undergoing MCAo for 60 minutes followed by IA administration of verapamil (2.5mg/kg) demonstrated significant reduction in infarct volume, astrocyte activation and apoptosis with a significant increase in mature neuron survival. Functional measures of forced motor and free roam movement showed significant differences on post-stroke day (PSD) 1, 3 and 5 for rotor rod and PSD 7 for open field between treated and control (Figure 2-4). Finally, we recently completed enrollment on a Phase I safety study of IA verapamil immediately following thrombectomy in 11 ELVO patients. The primary outcome measure of safety (no significant intracranial hemorrhage) was achieved in all patients.

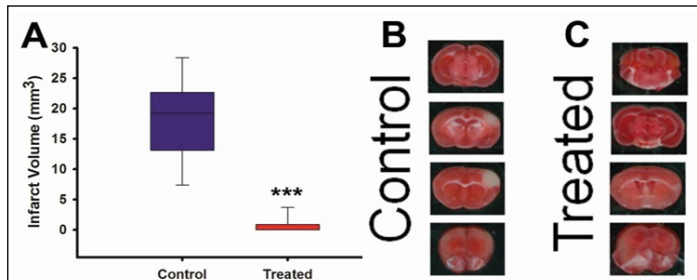


Figure 3. A. Infarct volume, control vs. treated. B. TTC image of control stroke. C. TTC image of treated stroke.

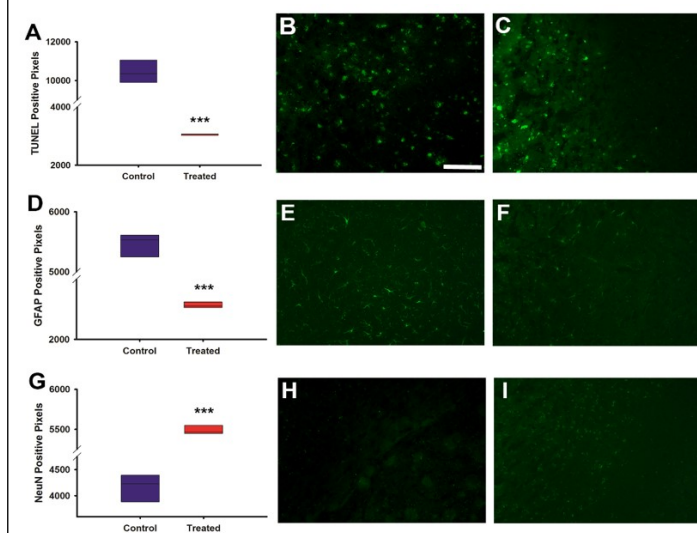


Figure 4. A. TUNEL positive pixel graph, Control vs. Treated., B. Control TUNEL., C. Treated TUNEL., D. GFAP positive pixel graph, Control vs. Treated., E. Control GFAP., F. Treated GFAP., G. NeuN positive pixel graph, Control vs. Treated., H. Control NeuN., I. Treated NeuN.

## Learning Objectives

Following this session, participants will be able to: 1) Describe verapamil's proposed mechanism of action in neuroprotection. 2) Identify verapamil as a potential neuroprotective compound when administered as an adjunct to thrombectomy for emergent large vessel occlusion.

## Conclusions

Therefore, intra-arterial verapamil represents a feasible, safe, and possibly therapeutic adjunct to thrombectomy in stroke. Further translational evaluation including dose-response and toxicity studies are planned, and will provide important translational data for adjunctive therapy in stroke.

## References

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- 3) Fransen PS, Beumer D, Berkhemer OA, van den Berg LA, Lingsma H, van der Lugt A, et al. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. *Trials*. 2014;15:343.
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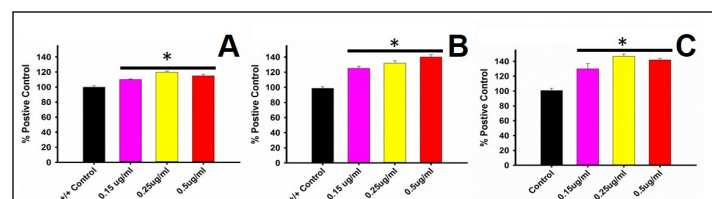


Figure 1. A. PC-12 OGD (2.5hr) with verapamil treatment., B. PC-12 OGD (5hr) with verapamil treatment., C. PC-12 OGD (6.5hr) with verapamil treatment. (N of 3, n of 6)

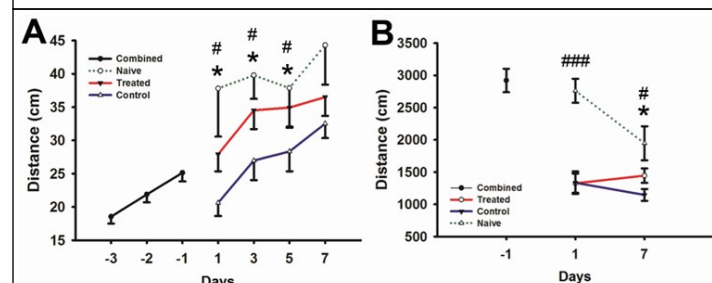


Figure 2. A. Rotor Rod forced motor movement. B. Open Field free roam movement