Pre-Clinical Middle Cerebral Artery Occlusion Ischemic Stroke Pig Model

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Introduction

Stroke is the leading cause of long term disability and third major cause of death in the United States. The devastating health, social and economic effects of stroke have led to a concerted effort to develop a treatment. Despite over 700 drugs going to human clinical trials, only one with significant therapeutic short comings has been approved by the Food and Drug Administration. An assessment of failed treatments by the Stem Cell Therapies as an Emerging Paradigm in Stroke group found that one of the likely major causes of failed translation is limited testing in large animal models more similar to humans. Our objective was to develop a pig middle cerebral artery occlusion (MCAO) ischemic stroke model to address this need. The pig is more similar to humans than rodent models with respect to brain gray-white matter composition, architecture and size likely making it a more predictive model and improving translatability. We hypothesize that cauterization of the MCA will lead to permanent occlusion of blood flow to the brain resulting in ischemic infarction, motor function deficits and behavioral dysfunction.

Materials and Methods

Ischemic injury was surgically induced in 8 male Yucatan miniature pigs by frontotemporal craniectomy on the right side of the head. The MCA was permanently occluded by bipolar electrocautery forceps. Magnetic resonance imaging (MRI) was performed at 24 hrs post-MCAO surgery on a 3.0 Tesla MRI system. Volumetric analysis was done on captured apparent diffusion coefficient (ADC) map images. Changes in gait (motor function) was assessed pre-stroke and post-stroke utilizing high speed cameras and gait analysis software. Histological analysis was performed at day 90 to determine cellular and structural changes.

Results

MRI analysis of MCA occluded animals after 24 hrs showed infarct volumes of 91.76 ± 21.70 cc and 10.56 ± 5.21 cc for 80% (Fig. 1A) and 40% (Fig. 1B) ADC thresholds respectively. Mean ADC value of normal control tissue of 731.75 ± 40.49 $\times 10^{-6}$ mm/s was significantly higher than 80% and 40% ADC means of 508.86 ± 31.01 $\times 10^{-6}$ mm/s and 320.43 ± 3.22 $\times 10^{-6}$ mm/s. Pre-stroke motor function analysis showed a high level of symmetry between left and right limb movement for maximum step height, stride length and stride velocity suggesting normal pig gait. However, analysis of these same parameters at days 1 and 30 post-stroke revealed significant asymmetry between right and left sides. Histological examination at day 90 through the area of infarction typically demonstrated severe atrophy of the affected right hemisphere. The white matter in the affected cortex region could not be defined due to loss of normal elements and showed glial proliferation and infiltration of gitter cells. These findings were in sharp contrast to the unaffected hemisphere.

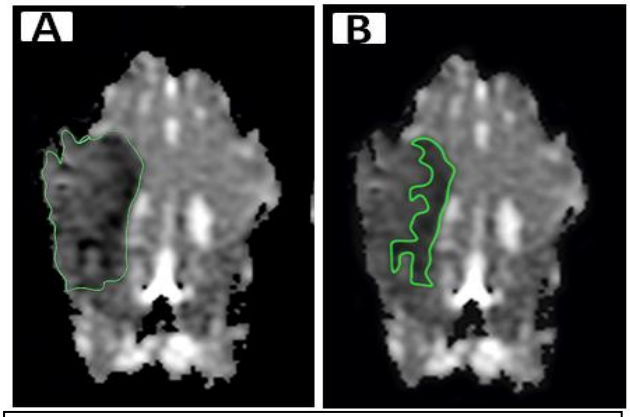

Fig. 1. ADC maps 24 hrs post-MCAO stroke show regions of 80% (A) and 40% (B) ADC thresholds.

Discussion and Conclusion

MRI, histological and gait analysis demonstrate severe brain infarction and loss of motor function indicative of a stroke. The development of a pig MCAO model will allow stringent assessment of efficacy and safety of cell therapies, therapeutics and devices in a large model that shares important anatomical and physiological features with humans.

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Disclosures

The authors have no conflict of interest.