Long-term follow-up of a rat model of transient ischemic stroke: protocol design and characterization of neurofunctional and imaging endpoints in the context of stem cell therapy

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Introduction: Stem cell therapy is a promising ischemic stroke treatment; however, there is little consensus regarding the most appropriate protocol and relevant endpoints for pre-clinical evaluation. The aim of the study was to design a protocol for the long-term assessment of stroke in a rat model of transient middle cerebral artery occlusion (tMCAO) using staircase task (ST) coupled with diffusion tensor imaging (DTI) **Methods:**25 male Sprague-Dawley rats were trained for the ST and then submitted to surgery. Stem cells were injected at week 1 (W1) in half of tMCAO rats. The ST was performed 4 times a week during 5 weeks. The number of pellets retrieved with forepaws were averaged to obtain one score per week. Side bias (SiB) was calculated as: contra/(ipsi + contra). MRI was obtained at D3 and D35 post-surgery. Lesion size was measured on T2-weighted imaging. The conventional DTI metrics (AD, RD, MD and FA) were measured in both striatum. **Results:** 10 rats were included, 6 tMCAO and 4 shams. The ipsilateral forepaw of tMCAO rats (corresponding to brain spared side) regained sham level at W2, while the contralateral showed prolonged deficits (SiB at W5: tMCAO 19±17% vs sham 51±5%, p=0.003). The lesion shrank between D3 and D35 (tMCAO: -39±37%). DTI metrics AD, RD and MD significantly increased at D35 in the ipsilateral striatum of tMCAO (for MD, D35, ipsi vs contralateral side: p=0.001). There was an inverse correlation between MD and SiB at W5 (R^2=0.87). There was no difference between treated and untreated group in ST (SiB at W5: treated 22±18% vs untreated 16±18%, p=0.34), lesion shrinkage (treated -52±17% vs untreated -26±51%, p=0.22) and DTI metrics (for MD; D35: p=0.28). **Conclusion:** We characterized neurofunctional and imaging endpoints for monitoring long-term outcome in tMCAO vs sham rats and checked the innocuity of intracerebral cell administration.