Effects of Dimethyl Sulfoxide on the evolution of ischemic penumbra using diffusion and perfusion imaging

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Introduction Dimethyl sulfoxide (DMSO) is widely used as a solvent for a variety of drugs and has a broad spectrum of biological activities that suggest efficacy as a neuroprotectant such as hydroxyl radical scavenging and Na^+-blocking activity. However, the beneficial effects of DMSO in the treatment of acute focal brain ischemia are not clearly delineated. Diffusion- (DWI) and perfusion-weighted (PWI) magnetic resonance imaging are powerful imaging modalities for early detection of cerebral ischemia. The region of ischemic brain with diminished perfusion but without altered diffusion characteristics (diffusion/perfusion mismatch) is thought to represent an approximation of the ischemic penumbra. We investigated the in vivo effects of intravenous DMSO on ADC and CBF characteristics in the core and mismatch region defined before treatment and on the spatio-temporal evolution of the ischemic lesion in a rat permanent ischemia model using quantitative diffusion and perfusion imaging.

Method Permanent focal ischemia was induced 18 Wistar rats (300-350g) using the intraluminal middle cerebral artery occlusion (MCAO) method. DMSO (1.5g/kg IV, n=9) or saline (n=9) were administered over 3 hrs starting 1 hr after MCAO. MRI data were acquired initially at 45 min (baseline), at 90 min after MCAO, and then every 30 min up to 4 hrs after occlusion. TTC-staining was performed 24 hrs after MCAO. MRI was performed on a 4.7T/40cm magnet. ADC was measured using spin-echo EPI with matrix = 64x64, FOV = 2x2cm^2, eight 1.5-mm slices, TE = 39ms, TR = 2s, 16 averages, b = 10 and 1270 s/mm^2 along each of the 3 principle axes. CBF was measured using the continuous arterial spin-labeling technique with single-shot, gradient-echo EPI, with parameters similar to the ADC measurement except TE = 15ms. Total, cortical and subcortical lesion evolution were derived using the CBF (0.30 ml/g/min) and the ADC (0.53 x10^{-3}mm^2/s) viability thresholds established previously in our lab. The effects of DMSO on the temporal evolution of the CBF and ADC characteristics of the initial core and mismatch regions, defined at 45 min before treatment, were also evaluated. On the initial ADC and CBF maps (45 min), ischemic damage was classified into the core area (ADC and CBF < thresholds) and the mismatch area (ADC > threshold, CBF < threshold). Subsequent ADC and CBF values were then prospectively measured in each area at each time point.

Results **Figure 1: Evolution of total ADC and CBF lesions**

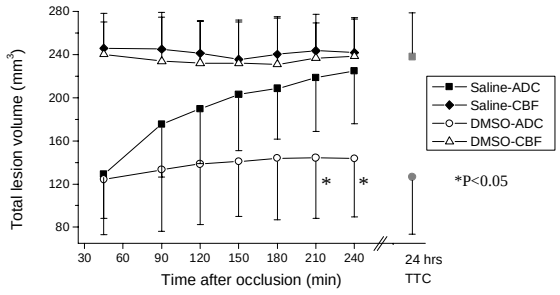


Figure 2: Evolution of cortical and subcortical ADC lesions

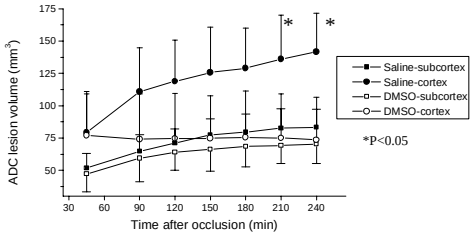


Figure 3: ADC characteristics in the core and mismatch area

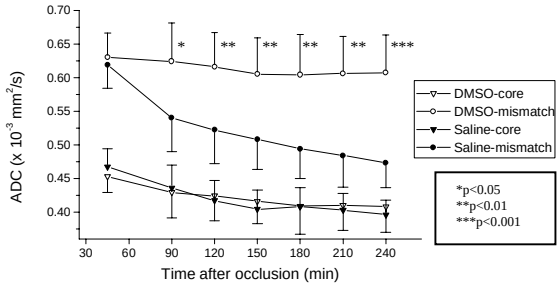
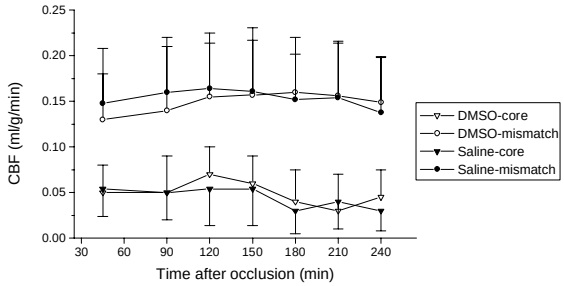


Figure 4: CBF characteristics in the core and mismatch area



Physiological variables including body temperature, pO_2, pCO_2, pH, and blood pressure were within normal range and did not vary among the two groups. CBF-derived lesion volumes remained relatively constant in both groups without significant changes across time. No significant differences were observed between groups at any time point (**Fig.1**). The initial ADC lesion volumes were essentially identical (**Fig.1**). However, while the ADC lesions continued to enlarge gradually over time in the untreated animals, lesion volumes in the DMSO treated group increased only slightly at 90 min and then largely stopped evolving (**Fig.1**). The treatment effect was maximal in the cerebral cortex as the cortical ADC-derived lesion volume completely stopped progressing during DMSO treatment (**Fig.2**). No significant differences in the evolution of the subcortical ADC lesions were observed (**Fig.2**). During the infusion, the mismatch volume in the DMSO group was similar at all time-points (ranging from 41 to 46% of the CBF-deficit) and the abnormal perfusion volume was significant larger than the abnormal diffusion volume at all time points ($P < 0.02$ each). In the control group, the difference between the abnormal perfusion and diffusion regions was only significant at 45 and 90 min after MCAO ($P < 0.0001$ and $P < 0.01$), and gradually decreased over time. By 4 hrs after occlusion, the abnormal diffusion volume was 94% of the abnormal perfusion volume.

Compared to the MRI lesion volumes at 4 hrs after MCAO, the TTC infarct volume in the control group was slightly larger than the ADC-derived lesion volume and essentially identical to the CBF-derived lesion. In the DMSO-treated animals, however, the TTC-defined infarct size 24 hrs after occlusion was virtually identical to the baseline ADC lesion before treatment (**Fig.1**).

In the non-ischemic left hemisphere (LH), the mean CBF and ADC values remained constant during the entire study period in both groups without significant differences between groups or different time points. The temporal evolution of ADC and CBF values in the core and mismatch regions, defined before treatment, were prospectively quantified (**Fig. 3 and 4**). At baseline, the ADC and CBF characteristics of the core and mismatch regions were comparable between the two groups. In the mismatch region, the mean ADC values in the control group continuously decreased over time. In the DMSO group, the ADC values in the mismatch area declined only slightly at 90 and 120 min and then remained constant up to 4 hrs after occlusion. The difference in mean ADC values between the DMSO and the control group was significant at all time points during treatment ($P < 0.05$ each). In the core region, no significant differences in the evolution of ADC values were observed between untreated and treated animals (**Fig. 3**). Region-specific CBF characteristics did not differ significantly between the two groups at any time point ($P > 0.05$, **Fig. 4**).

Conclusions IV DMSO resulted in a robust neuroprotection in a reasonable time window without observable side effects in this permanent ischemia model. In vivo imaging indicated that DMSO exerted its effects by preserving the diffusion/perfusion mismatch without altering cerebral hemodynamic characteristics. Our data suggest that DMSO represents an interesting candidate for acute stroke therapy.