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Title 論文題目	Intravenous infusion of mesenchymal stem cells enhances therapeutic efficacy of reperfusion therapy in cerebral ischemia. (脳虚血に対する再開通療法の治療効果を経静脈的骨髄間葉系幹細胞移植療法は高める。)
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**Intravenous infusion of mesenchymal stem cells enhances therapeutic efficacy of
reperfusion therapy in cerebral ischemia**

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Running head: Infused MSCs enhance therapeutic efficacy of reperfusion therapy

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ABSTRACT

OBJECTIVE: Reperfusion therapy is a standard therapeutic strategy for acute stroke. Non-favorable outcomes are thought to partially result from impaired microcirculatory flow in ischemic tissue. Intravenous infusion of mesenchymal stem cells (MSCs) reduces stroke volume and improves behavioral function in stroke. One suggested therapeutic mechanism is the restoration of the microvasculature. The goal of this study was to determine whether infused MSCs enhance the therapeutic efficacy of reperfusion therapy following stroke.

METHODS: First, to establish a transient middle cerebral artery occlusion (MCAO) model displaying approximately identical neurological function and lesion volume as seen in permanent MCAO (pMCAO) at day-7 after stroke induction, we transiently occluded the MCA for 90, 110, 120 min. We found that the 110 min-occlusion met these criteria and was used as the transient MCAO (tMCAO) model. Next, four MCAO groups were used to compare the therapeutic efficacy of infused MSCs: (1) pMCAO+vehicle, (2) tMCAO+vehicle, (3) pMCAO+MSC and (4) tMCAO+MSC. Our ischemic model was a unique ischemic model system in which both pMCAO and tMCAO provided similar outcomes during the study period in the groups without MSC infusion groups. Behavioral performance, ischemic volume, and regional cerebral blood flow (rCBF) using arterial spin labeling (ASL)-magnetic resonance imaging and histological evaluation of microvasculature was performed.

RESULTS: The behavioral function, rCBF, and restoration of microvasculature were greater in group 4 than in group 3. Thus, infused MSCs facilitated the therapeutic efficacy of MCA reperfusion in this model system.

CONCLUSIONS: Intravenous infusion of MSCs may enhance therapeutic efficacy of reperfusion therapy.

KEY WORDS: mesenchymal stem cell, stroke, reperfusion, intravenous

ABBREVIATIONS:

MCA, middle cerebral artery; tMCAO, transient MCA occlusion; pMCAO, permanent MCA occlusion; MSC, mesenchymal stem cell; DWI, diffusion-weighted imaging; rCBF, regional cerebral blood flow; ROI, region of interest; FITC, fluorescein isothiocyanate; mRS, modified Rankin scale; DMEM, Dulbecco's modified Eagle's medium; ASL, arterial spin labeling; MRI, magnetic resonance imaging; CD, cluster of differentiation; TOF, time-of-flight; MRA, magnetic resonance angiography