

# MRI of Acute and Delayed Administration of Marrow Stromal Cells in Rats with Traumatic Brain Injury

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**Background and Purpose:** Cell transplantation has potential as an effective therapeutic strategy to attenuate secondary injury after traumatic brain injury (TBI) that diffusely affects brain. While promising, several key issues regarding optimization of basic transplantation techniques remain to be addressed. One of these issues is timing of transplantation<sup>1</sup>. Using MRI, the objective of the present study was to test the hypothesis that acute engraftment of human marrow stromal cells (hMSCs) into the brain subjected to TBI provides an advanced therapeutic effect as compared to delayed transplantation.

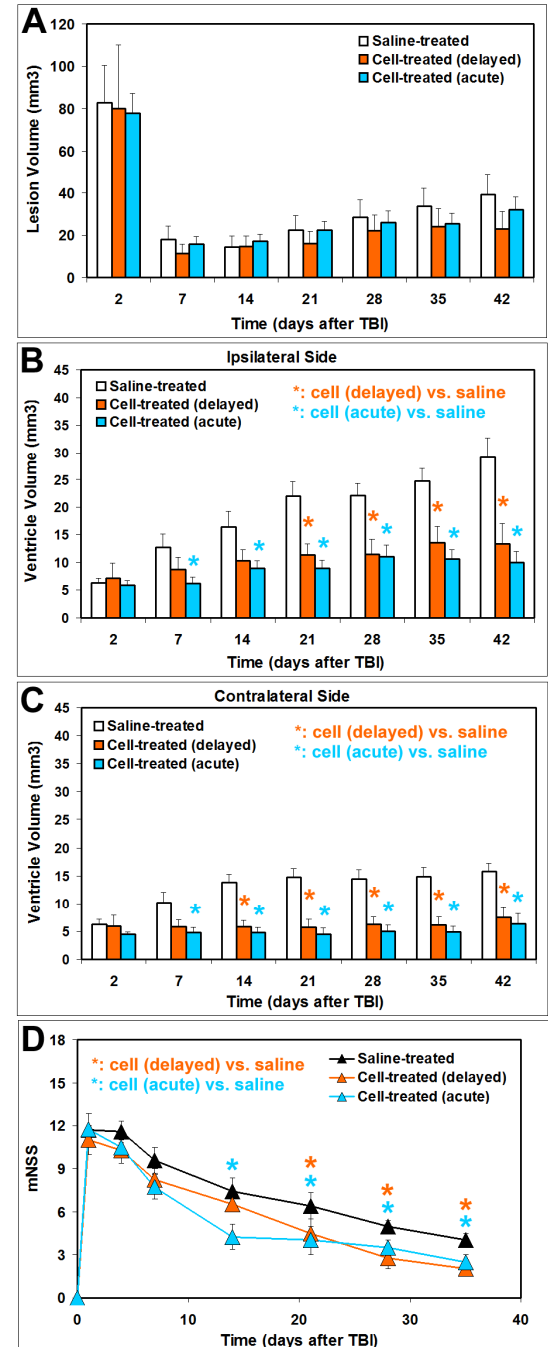
**Materials and Methods:** Male Wistar rats (300-350g, n=28) subjected to controlled cortical impact TBI were intravenously injected with 1 ml of hMSCs in suspension ( $3 \times 10^6$  hMSCs) 6 hours (acute, n=9), 5 days (delayed, n=9) post-TBI or with 1 ml of saline at acute and delayed time point, respectively (n=5 for each time point). *In vivo* MRI acquisitions of T2-weighted imaging (T2WI), three-dimensional (3D) gradient echo imaging and blood-to-brain transfer constant (Ki) of contrast agent were performed on all animals 2 days post-injury and weekly for 6 weeks. Sensorimotor function was evaluated with modified neurological severity score (mNSS). Both 3D images and T2 maps were used to identify cortical lesion and lateral ventricle in the ipsilateral side of the brain<sup>2</sup>. Volumetric changes in the trauma-induced brain lesion and the lateral ventricles were tracked and quantified using T2 maps, and blood-brain barrier (BBB) permeability was monitored by Ki. Hyperintensities on Ki map representing angiogenesis<sup>3</sup> were distinguished from elevated areas indicating BBB damage by their distinct temporal and spatial profiles, and were confirmed by histological evaluation (presence of enlarged thin-walled vessels on EBA-stained tissue slice).

**Results:** No significant differences in MRI measurements and functional outcomes between the acute and delayed saline-treated group were detected. Thus, all animals with saline injection post-TBI were considered as a saline-treated group. Neither acute nor delayed intervention of hMSCs significantly diminished lesion volume over a 6-week observation period (Fig. 1A). Treatment with hMSCs significantly reduced ventricular dilation (Fig. 1B-1C,  $p < 0.05$ ) in both the ipsilateral- (Fig. 1B, 1 to 6w for acute group; 3 to 6w for delayed group) and contralateral-side (Fig. 1C, 1 to 6w for acute group; 2 to 6w for delayed group) of the brain, suggesting that hMSCs reduce cerebral atrophy. Neurological severity score (mNSS) in the saline-treated animals was significantly higher than in the cell-treated animals (Fig. 1D,  $p < 0.05$ , 2 to 5w for acute group; 3 to 5w for delayed group). Administration of hMSCs led to an early presence of angiogenesis in the trauma-injured brain (estimated median time: 2, 3 and 4w post-injury for acute-, delayed- and saline-treated group, respectively). Ki-detected angiogenesis occurred significantly earlier in the acute cell-treated group ( $p < 0.05$ ), and not in the delayed cell-treated group ( $p > 0.05$ ), compared to the saline-treated group.

**Discussion and Conclusions:** Our data demonstrate a wide intravenous intervention window of MSC therapy for TBI. However, the significant therapeutic effects of hMSC treatment on reduction of ventricular expansion (Fig. 1B-1C) and decrease of mNSS (Fig. 1D) were present at earlier time points after acute transplantation (1 to 2w) than after delayed engraftment (2 to 3w). These data suggest that acute cell intervention extends the time range of therapeutic benefit by initiating the therapeutic effects earlier. Also, acute engraftment evokes angiogenesis in the injured brain, which occurs early and likely plays an important role in enhanced post-injury brain remodeling. While delayed cell transplantation may avoid the time period of intense inflammatory response of the trauma-injured brain, our data suggest that acute MSC administration after TBI provides an enhanced protective and therapeutic effect compared to delayed transplantation.

## References:

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**Fig. 1** Volumetric changes in cortical lesion (A) and lateral ventricles (B and C) identified on T2 map, and line graphs (D) illustrating functional outcome after TBI.