Transplantation of Marrow Stromal Cells Restores Cerebral Blood Flow and Reduces Cerebral Atrophy in Rats with Traumatic Brain Injury: in vivo MRI Study

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Background and Purpose: Cell therapy has been demonstrated to promote brain remodeling and improve functional recovery after various central nervous system disorders, including traumatic brain injury (TBI)[1-2]. However, little is known about the dynamic effect of grafted cells on post-TBI hemodynamic and atrophic progression. The present study was designed to test the hypothesis that engraftment of human marrow stromal cells (hMSCs) into the brain subjected to TBI provides therapeutic benefit in modifying cerebral hemodynamic and structural abnormalities, which are detectable by *in vivo* MRI.

Materials and Methods: hMSCs were labeled *in vitro* with superparamagnetic iron oxide (SPIO) nanoparticles[3]. Male Wistar rats (300-350g, n = 18) subjected to controlled cortical impact TBI were intravenously injected with 1 ml of saline (n = 9) or hMSCs in suspension (n = 9, approximately $3x10^6$ SPIO-labeled hMSCs) 5 days post-TBI. *In vivo* MRI measurements consisting of cerebral blood flow (CBF), T2-weighted imaging and 3D gradient echo imaging were performed for all animals 2 days post-TBI and weekly for 6 weeks. Functional outcome was evaluated with modified neurological severity score (mNSS) and Morris water maze test. Cell engraftment was detected *in vivo* by 3D MRI and confirmed by Prussian blue staining. Ventricle and lesion volumetric alterations were measured using T2 maps[3-4] (**Fig. 1**, **Fig. 2**), and hemodynamic abnormality was tracked by MRI CBF measurements (**Fig. 3**).

Results: 3D MRI and Prussian blue staining demonstrated that SPIO-labeled hMSCs primarily localized adjacent to the lesion site. The temporal profiles of lesion volume depicted on T2 map were similar for two treatment groups (**Fig. 1E**), with a large edematous tissue volume appearing acutely, then rapidly decreasing to a focal lesion within 1 week and slightly extending from 1 to 6 weeks. No significant group difference in T2 lesion volume was found over a 6-week observation period. Saline-treated animals had significantly larger ventricle in the ipsilateral- (**Fig. 2I**, 3 to 6w, $p < 0.01$), contralateral- (**Fig. 2J**, 2 to 6w, $p < 0.002$) and both-side (**Fig. 2K**, 2 to 6w, $p < 0.01$) of the brain after TBI than cell-treated animals. Treatment with cell transplantation significantly reduced both the magnitude ($p < 0.01$) and rate ($p < 0.04$) of ventricular expansion after TBI (**Fig. 2K**). While the area with lower CBF extended beyond the location of primary impact site (**Fig. 3D-F**), treatment with cell transplantation restored and preserved CBF in the brain regions adjacent to and remote from the lesion (**Fig. 3A-C**) at a later stage of TBI. Significantly larger area with abnormal CBF value (lower than 30mL/100g/min) was detected in the saline-treated group than in the cell-treated group at later stage of TBI (**Fig. 3G**, 4 to 6w, $p < 0.04$). Significantly higher mNSS numbers were awarded to the saline-treated animals than to the cell-treated animals (3 to 5w, $p < 0.05$). The cell-treated animals spent significantly longer time in the correct quadrant than the saline-treated animals (33 to 35d, $p < 0.05$).

Conclusion: Treatment with hMSCs following TBI diminishes hemodynamic abnormalities by early restoration and preservation of CBF in the brain regions adjacent to and remote from the impact site, and reduces generalized cerebral atrophy, all of which may contribute to the observed improvement of functional outcome.

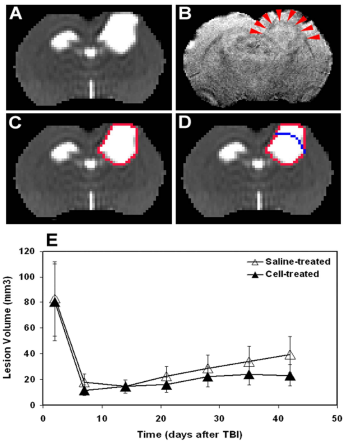

Fig. 1 A representative saline-treated animal with connected cortex lesion and expanded lateral ventricle after TBI detected by T2 map (A) and corresponding 3D image (B), and quantitative results (E). It was impossible to distinguish between lesion and ventricle on T2 map alone (C). However, the anatomical information revealed by 3D image (B, corpus callosum, red arrowheads) provided a border line (D, blue line) that divided the hyper-intense area identified on T2 map (C) into two regions, upper cortex lesion and lower expanded ventricle (D).

References:

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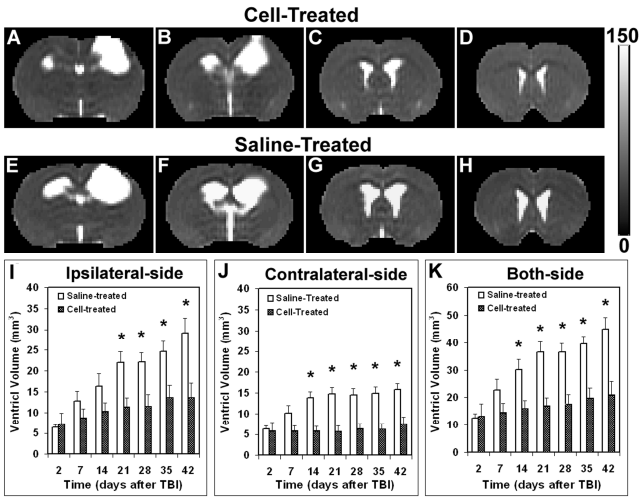

Fig. 2 Comparison of lateral ventricle (6 weeks post-TBI) presented by 4 consecutive T2 slices (A-D: cell-treated animal; E-H: saline-treated animal) and quantitative results (I-K).

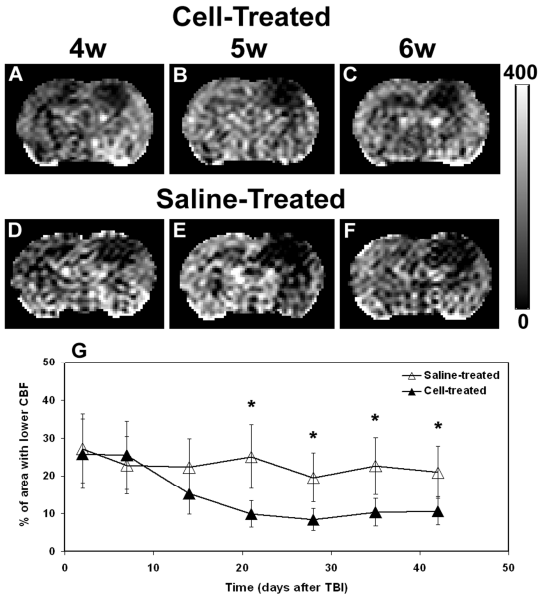

Fig. 3 Illustrative comparison of CBF maps shown in representative animals (A-C: cell-treated animal; D-F: saline-treated animal) and quantitative results (G).