BOLD activation pattern for motor task in chronic stroke patients after administration of autologous mononuclear and mesenchymal stem cells

A. Bhasin[1], S. Senthil Kumaran[2], M. V. Padma[1], S. Mohanty[3], and R. Bhatia[1]

[1]Department of Neurology, All India Institute of Medical Sciences, New Delhi, India, [2]Department of N.M.R, All India Institute of Medical Sciences, Delhi, India, [3]Stem Cell Facility, All India Institute of Medical Sciences, New Delhi, India

Introduction: Stroke is the second leading cause of disability in India[1]. The restoration of function in stroke is aimed by stem cell transplantation as these cells are feasible, multi-potential and have homing in properties[2]. They are known to repair brain after stroke by replacing the dead cells, enhancing neurogenesis and modulating the host environment[3]. The aim of this study was to observe safety, feasibility and efficacy of bone marrow mononuclear and ex vivo expanded mesenchymal stem cells on clinical scores and functional imaging methods.

Methods: Twenty (n=20) chronic stroke patients were recruited from the neurology clinics with the inclusion criteria 18-70 years of age, MRC grade for wrist and hand muscles atleast > 2, NIHSS scale between 4 and 20, between 3 months to two years of stroke onset, conscious and be able to comprehend. 50-60 ml of bone marrow was aspirated under aseptic conditions. The mean culture time for mononuclear stem cells (MNC) was 150±20 minutes which were administered to fourteen patients (n=14), whereas the expansion of mesenchymal (MSC) took 23±5 days which were administered to six patients (n=6). Each patient was infused with $5x10^8$ cells in 250 ml saline intravenously over a duration of 150±10 minutes. The functional MRI was performed at baseline and 24 weeks. The motor task used was either fist making or extension of the wrist, depending upon the compliance of the subject. Block design with alternate baseline and activation task was used with a total of 90 whole brain EPI measurements (TR =4520 ms, TE =44 ms, slices =31, slice thickness =4 mm). The studies were carried out on 1.5 T MR system (Avanto, M/s Siemens, Erlangen, Germany) using head coil. Ten age matched healthy controls were recruited for comparison with stroke patients.

Results: The clinical, laboratory and radiological reports were normal in all patients and did not report any serious adverse events till 24 weeks follow up. There was no statistical significant difference in the clinical scores between MNC and MSC groups at 24 weeks ($p>0.05$). There was a significant increase in the number of voxels in the Brodmann area (BA 6) at 24 weeks in all the patients ($p>0.05$). There was a considerable increase in the laterality index (LI) of ipsilesional cortex. When BOLD activation was compared between MNC with respect to MSC group, we observed an activation of 63 voxels in right BA 6, 101 voxels in right BA 35 (Table 1, Figure 1). When MSC group were compared to MNC group, we observed an activation of 44 voxels in right BA 6, 25 voxels were active in right BA 40. On comparison between the stem cell group and healthy controls, it was observed that premotor and inferior parietal areas were active with cluster counts of 65 and 56 respectively in the stem cell group (Table 2, Figure 2).

Table 1. BOLD activation MNC with respect to MSC in right hemispheric stroke

Cluster	Z score	mni coordinates (x,y,z) mm	Hemisphere	Area of activation	Brodmann Area
95	4.69	-50 0 -8	Left	STG	BA 38
63	4.55	-32 38 60	Right	MFG	BA 6
101	4.44	-20 -18 -12	Right	PHG	BA 35
34	3.90	-2 26 24	Left	AC	BA 24
40	2.78	8 -58 6	Right	LG	BA 18

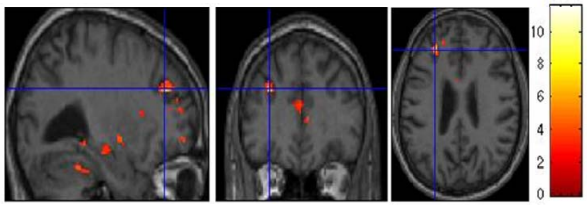

Figure 1. BOLD activation MNC with respect to MSC in right hemispheric stroke overlaid on anatomical images.

Discussion: Intravenous stem cell transplantation is safe and feasible in chronic stroke patients. Both the groups showed improvements clinically and radiologically although it was not conclusive which type of cells are efficacious. With an increased number of voxels recruited in premotor, primary motor cortex, inferior parietal lobule and hippocampal gyrus at follow up, we can attribute that stem cell therapy leads to cortical re-organisation[4,5] . The 'restitution' principle of plasticity can be supported by an increased activation of motor cortex (injured) in the stem cell group when compared with healthy controls[6,7].

Table 2. BOLD activation in MNC and MSC in right hemispheric stroke with respect to healthy controls

Cluster	Z score	mni coordinates (x,y,z) mm	Hemisphere	Area of activation	Brodmann area
65	3.45	22 4 66	Right	MFG	BA 6
141	3.60	-20 18 6	Left	CG	BA 32
56	3.15	-52 -32 28	Right	IPL	BA 40

STG: superior temporal gyrus, MFG: middle frontal gyrus, AC: anterior cingulate, LG: lingual gyrus, PHC: parahippocampal gyrus, CG: Cingulate Gyrus, IPL: Inferior Parietal Lobule

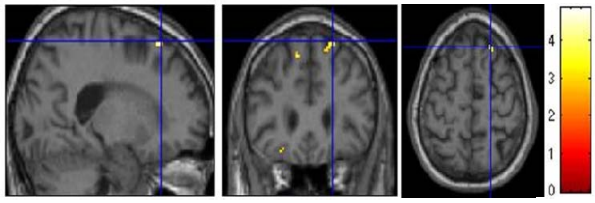

Figure 2. BOLD activation in stem cell group with respect to healthy controls overlaid on anatomical images.

References:
1. Banerjee TK, Mukherjee CS, Sarkhel A. 2001 Neuroepidemiology. **20:**201-207.
2. Raff M, et al. 2003 Annu Rev Cell Dev Biol **19:**1-22.
3. Kopen GC, Prockop DJ, Phinney DG, et al. 1999 Proc Natl Acad Sci USA **96:**1016-71.
4. Brennemann M, et al. 2010 Journal of Cerebral Blood flow and metabolism **30:**140-149.
5. Feydy A, et al. 2002 Stroke **33**:1610-1617.
6. Lindvall O, Kokaia Z, et al. 2004 Stroke **35:**2691-2694.
7. Yong Y, Xiao-xi Z, et al. 2007 Chin J Evid based Med**. 7:**743-749.