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Cellular Therapy Improves Brain Metabolism in a Case of Chronic Ischemic Stroke

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ABSTRACT

Objective: Cellular therapy is an emerging therapeutic option for chronic stroke. The aim of this report was to study the effect of autologous bone marrow mononuclear cells followed by neurorehabilitation in the case of chronic ischemic stroke.

Method and results: The patient was a 50-year-old male suffering from ischemic stroke due to middle cerebral artery infarct since 4 years. The intervention included intrathecal administration of autologous bone marrow mononuclear cells followed by neurorehabilitation. He presented with right hemiparesis, dysarthria and memory deficits. He underwent cellular therapy twice at an interval of 6 months. Post cellular therapy the voluntary control, memory, ambulation and speech improved. The recovery was also marked by an improvement on Berg Balance scale (50 to 52), Beck Depression Inventory scale (23 to 9) and the Reach score. Comparative Positron Emission Tomography-Computer Tomography (PET CT) scan of brain 6 months after cellular therapy showed improvements in bilateral frontal cortex, parietal cortex, thalamus, cerebellum, medial temporal cortex, right basal ganglia, right temporal cortex, cingulate cortex which correlated with clinical improvements.

Conclusion: Cellular therapy along with neurorehabilitation was safe and beneficial. Cellular therapy assisted the impaired areas of brain in recovery as demonstrated on PET CT scan even at a chronic stage. To understand the efficacy of the cellular therapy further randomised controlled clinical trials should be conducted.

Key words: Stroke, Cellular therapy, Brain injury, Stem cells, bone marrow mononuclear cells, autologous, PET CT.

INTRODUCTION

Stroke is a condition that occurs when the supply of blood to the brain is interrupted due to blockage or rupture of a blood vessel, resulting into damage to the nervous tissue. The primary site of injury is called 'umbra' and the secondary having partially viable neuronal cortex is called 'penumbra'. [1] Stroke is a leading cause of death and major source of disability in adults. [2]

Stroke is a disorder for which clinically effective therapeutic modalities are most needed and various ways have been explored to investigate their feasibilities. However, curative treatment for stroke is not available. [3] Recovery after stroke is determined by the site, extent of lesion and time. Present management of stroke aims at restoring blood flow and maintaining tissue perfusion through various techniques which include anticoagulants, antiplatelet aggregation agents or thrombolytic agents. [4] Most commonly used is recombinant tissue plasminogen activator (rt-PA) to breakdown blood clots. [5] However, these strategies lack desired effectiveness in preventing long term complications, have side effects and the recovery is incomplete.It is urgent to be able to provide a fundamental treatment to regenerate and prevent further damage of

neuronal cells. Hence, the use of stem cells for chronic stroke could be a breakthrough development.

Cellular therapy has been postulated as a beneficial therapeutic option for chronic stroke by promoting functional recovery through angiogenesis, neurogenesis and enhance neuroplasticity. [6] Stem cells are immature cells characterized by their ability to proliferate and/or differentiate into specialized cells in the host tissue. [7] Animal studies have revealed that Bone Marrow Mononuclear Cells (BMMNCs) transplantation for stroke leads to functional and neurological recovery. [8-12] A study using mouse model has revealed that intrathecal administration of stem cells by lumbar puncture was useful and feasible for treatment of stroke. [13] Similarly, studies in humans also support the safety and efficacy of intrathecal administration of stem cells for stroke. [14-19] It is important to study the changes at the cellular level after cell transplantation. Here, in this case we have used PET CT scan as a monitoring tool.

The following case study discusses the safety and efficacy of cellular therapy in a 4 years old chronic ischemic stroke patient.

CASE PRESENTATION

A 50-year-old male was diagnosed with right hemiparesis due to acute ischemic stroke secondary to left middle cerebral artery (MCA) territory infarct 4 years ago. The ischemic episode started with weakness, speech problem and sensory loss in the right side of the body and loss of consciousness for 20 hours. He was hospitalized for 10 days followed by regular rehabilitation. His ambulation had improved as he could walk with the help of cane and right hip hiking, minimum knee hyperextension and foot drop. Memory also improved partially. But, despite regular rehabilitation, there were no further improvements. He still had complaints of slurred speech, difficulty in using right upper limb for functional activities, stiffness in the fingers, memory deficits, difficulty in walking and stair climbing. Due to these complaints, he decided to explore new treatment.

At assessment prior to cellular therapy, he was hypertonic with grade 1+ on Modified Ashworth Scale (MAS) in right upper limb and lower limb. Right upper and lower limb showed flexor synergy pattern. Voluntary control of the right shoulder, elbow, hip, knee and trunk was fair whereas it was poor in wrist, hand, ankle and foot. Sitting balance was good whereas standing and walking balance was affected. Speech, attention, memory and hand functions were affected. Right upper limb overhead activity was affected as his upper body dressing required assistance. He couldn't chew food properly. He was ambulatory with the help of stick. Gait analysis showed right hip hiking gait pattern with minimum knee hyperextension. Functionally, he had modified independence for ADLs. Berg Balance scale (BBS) score was 50/56. Functional independence measure (FIM) score was 113. Beck depression inventory score was found to be 23. The score on the Modified Rankin scale (MRS) was found to be 3. Magnetic Resonance Imaging (MRI) of brain with diffusion tensor imaging (DTI) revealed severe gliotic changes involving the left frontotemporal lobes and gangliocapsular region. The flow void of the left intracranial (ICA) was obliterated, representing occlusion. PET CT scan of brain showed hypo metabolismin left frontal cortex, parietal cortex, cingulate cortex (anterior cingulate cortex, posterior cingulate cortex), temporal cortex, basal ganglia, thalamus, and right cerebellum.

MATERIALS AND METHOD

Considering his neurological and functional status 4 years after-stroke, he was enrolled for intervention using intrathecal administration of autologous bone-marrow-derived mononuclear cells followed by intensive rehabilitation. The patient was selected for intervention based on the inclusion criterion as per the World Medical Associations Helsinki declaration. [20] The

protocol for treatment was approved by the Institutional Committee for Stem Cell Research and Therapy (IC-SCRT). Detailed examination and assessments were conducted before cellular therapy, at the time of discharge (i.e., one week after-stem cell administration) and at follow-up visits A signed informed consent from the patient was obtained. Granulocyte colony stimulating factor (GCSF) was administered 72 hours and 24 hours before the harvest and transplantation of BMMNCs. [21] Bone marrow (110mL) was aspirated from the iliac bone under local anaesthesia. Mononuclear cells (MNCs) were separated using a density gradient method in the neural tissue laboratory. A viable count of the isolated MNCs was taken and the percentage of CD34+ cells was checked by fluorescence-activated cell sorting (FACS) analysis. Percentage of CD34+ cells was identified using PE antibody which was 4.28%. A total of 2.4×10^8 cells were transplanted intrathecally with a viability of 98%. MNCs were then injected intrathecally into cerebrospinal fluid at the space between 4^{th} and 5^{th} lumbar vertebra via a lumbar puncture. Solu-Medrol 1 gm in 500 ml Isolyte P was given intravenously simultaneously during the injection to reduce immediate inflammation post transplantation. Cellular therapy was followed by neurorehabilitation including physiotherapy, occupational therapy, and psychological counselling. Physiotherapy was done to improve voluntary control, balance and to normalize the tone. To improve trunk mobility, voluntary control, gross motor coordination and normalize the tone occupational therapy was done. FIM, BBS, Beck Depression Inventory, reach test Forward/Backward/Right/Left (F/B/R/L), MRS were the outcome measures used. As there were improvements after 1^{st} transplantation, he underwent the procedure for the second time 6 months after 1^{st} cell therapy. The patient was followed up at three months and 1 year after 2^{nd} intervention. The procedure was identical as the previous dose. 1.10×10^8 cells were injected for the 2^{nd} time with 98% viability. Percentage of CD34+ cells was 2.34%. Before and after transplantation, a 15min static Positron Emission Tomography–Computed Tomography (PET - CT) scan of the brain using the radioisotope 18 - F FDG (fluorodeoxyglucose) was performed on a Siemens Biograph HD MDCT with LSO detector technology. Brain glucose metabolism was measured using high-resolution PET/CT camera. Images were reconstructed using standard vendor-supplied software. The PET/CT images were visually interpreted by an expert. The data was compared with the normal healthy data base on a voxel by voxel basis for quantitative analysis.

RESULTS

Functional and clinical assessment was done at the time of discharge (i.e., one week after 1^{st} cell transplantation), no adverse effects were noted.

At three months follow-up after 1^{st} intervention, his standing and dynamic balance improved. He could walk more confidently on uneven surfaces. Speech improved and his speed in rolling increased. The voluntary control of shoulder, hip, knee and ankle was improved to fair plus. Berg balance score showed an increase from 50 to 52. FIM score was maintained but qualitative changes were seen. He was unable to perform the reach test. The score at Modified Rankin scale was found to be 3. (Table: 1)

At six months follow up after the 1^{st} intervention, the speech was better and the words were clearer. Oromotor skills had improved. He could chew food properly. Reach score (F/B/R/L) was found to be 4/3/2/2 inches. Berg balance score was 52.FIM and MRS was maintained. (Table:1)

Comparison of PET CT scan 6 months following 1^{st} cellular therapy showed significant improvement in bilateral frontal cortex (FC), parietal cortex (PC), right BG, right TC, cingulate cortex (ACC-anterior cingulate cortex, PCC- posterior cingulate cortex), mildly in bilateral

thalamus, medial temporal cortex and bilateral cerebellum (C). (Figure:1).

At three months, after 2nd cell transplantation his functional status was maintained. His upper limb overhead activity was improved. Memory had improved. BBS, MRS and FIM were maintained. Reach score (F/B/R/L) improved to 10/4/5/6 inches. Beck depression inventory score improved to 9. (Table:1)

At 1 year, after 2nd cell transplantation his functional status was maintained. His muscle tone had improved as stiffness in the fingers reduced. FIM and MRS were maintained. No new complaints or neurological worsening were reported in patient.

Table1: Scores of various outcome measures before and after cellular therapy.

Outcome measures	Score at assessment	Score at 3 months past 1st cellular transplantation	Score at 6 months past 1st cellular transplantation	Score at 3 months past 2st cellular transplantation
Functional independence measure(FIM)	113	113	113	113
Bergs Balance Scale(BBS)	50	52	52	52
Beck Depression Inventory	23			9
Reach test in inches (F/B/L/R)	Unable to perform	Unable to perform	4/3/2/2	10/4/5/6
Modified Rankin scale (MRS)	3	3	3	3

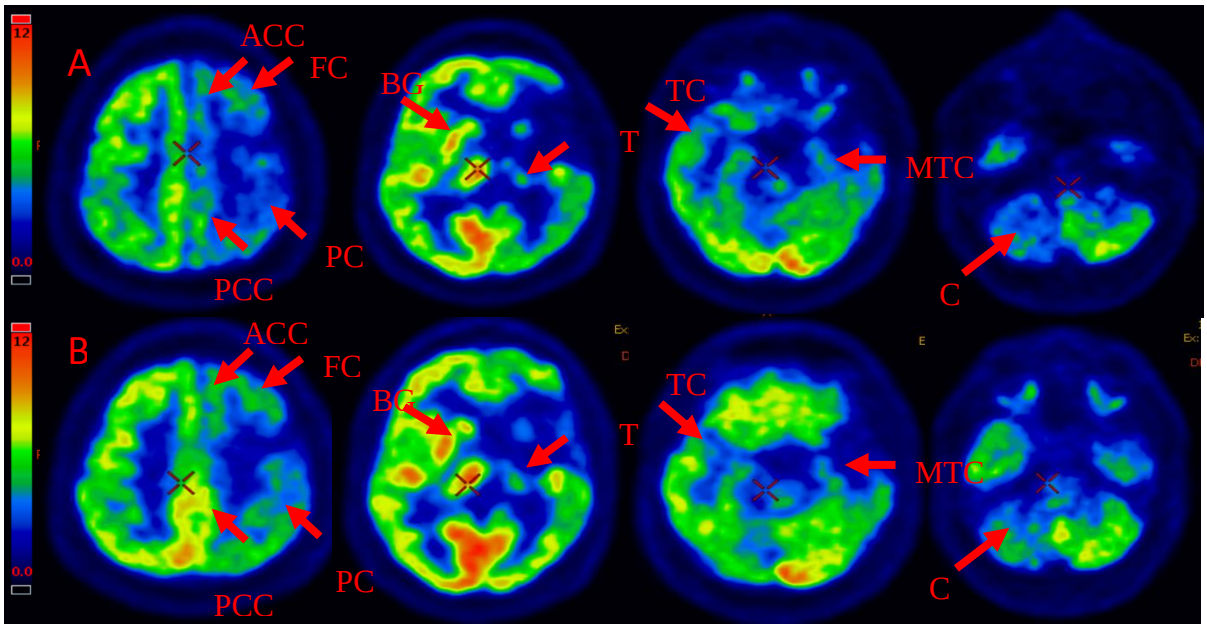

Figure 1: Representative Trans-axial cross-sectional PET CT image of the patient.

A] The PET CT scan before cellular therapy showed hypo metabolism in the left frontal cortex (FC), parietal cortex (PC), cingulate cortex (ACC- anterior cingulate cortex, PCC- posterior cingulate cortex), temporal cortex (TC), basal ganglia (BG), thalamus (T), and right cerebellum (C).

B] The Post PET scan following cellular therapy showed significant improvement in the bilateral frontal cortex (FC), parietal cortex (PC), right BG, right TC, cingulate cortex (ACC- anterior cingulate cortex, PCC- posterior cingulate cortex), mildly in bilateral thalamus, medial temporal cortex and bilateral cerebellum (C).

DISCUSSION

Stroke is a main cause of death and disability worldwide. The conventional management strategies in stroke include rehabilitation and medication such as thrombolytic agents have been

recommended, but still many patients live with enduring deficits. [22] Thus, there is need for alternative treatment strategies to address the underlying neurological deficits. Cellular therapy has been presented as a promising new modality for enhancing neurological recovery in chronic stroke. [23]

In this case prior to the cellular therapy, the patient had shown partial recovery with rehabilitation in memory and ambulation but was still dependent for his ADLs. Thus, by the combination of cellular therapy and rehabilitation, we aimed at activating brain rejuvenation and reperfusion through stimulation of regenerative mechanisms such as vasculogenesis, neurogenesis, angiogenesis, and synaptogenesis. The main objective of the restorative therapies is based on the concept of reorganizing brain, promoting implicit learning in the area with the lesion. Initially, it was thought that cellular therapy might work by 'cell replacement' mechanism, however recently a good amount of evidence has emerged suggesting that cellular therapy works by providing trophic or 'chaperone' support to the injured tissue and brain through its paracrine effects. [24]

Preclinical study of bone marrow mononuclear cell transplantation has demonstrated that they migrate to the peri-infarct area, enhance recovery, and modulate the post-ischemic inflammatory response. [10] Another study reported that intravenous administration of BMMNCs after stroke results in decreased infarct volume and good functional recovery in rats. [11] Intra-arterial administration of BMMNCs leads to a decrease in ischemic damage and good functional recovery in rat model. [12]

In our case study, Autologous BMMNCs was used because of several useful advantages including; easily obtained from bone marrow, the potential of autologous transplantation, no need for immunosuppressive regimes, lack of ethical or moral issues, no tumorigenicity and no genetic abnormalities. [25,26] Rat studies have revealed that intravenously, very few cells reach the damaged site as most of the cells are trapped by the lungs, liver and spleen whereas intraarterial infusion was accompanied by high incidence of microocculusion and intracerebral administration is invasive and has high risk. [27,28] The intrathecal route of administration is focused as it directly inserts the cells into the cerebrospinal fluid (CSF) and the cells are mobilized directly to the damaged part. Administration intrathecally is easy and devoid of any major side effects. [29] The G-CSF helps in the stimulation of the CD34+ cells and survival as well as multiplication of the stem cells. [30] In chronic stage, rehabilitation plays an important role in facilitating functional recovery through neuro-plasticity. [31]

PET CT is a non-invasive, functional imaging tool which studies the correlation of changes in the metabolic activity of the brain with the activity of the nervous tissues. [32] PET CT uses [18F]-fluoro-2-deoxy-Dglucose (18 FDG) dye, a glucose analogue which provides functional information of the cell based on glucose uptake. Preclinical and clinical PET studies with (18F-FDG) have consistently revealed a decreased 18F-FDG uptake in regions of presumed ischemic core. [33]

Ischemic stroke disrupts the blood circulation leading to brain injury and hampers the metabolism of neurons. This eventually leads to the cell death and impairment in the brain function. [34,35] The autologous bone marrow mononuclear cells exert therapeutic benefits by migrating to the injured site and protecting the nervous tissue from further injury and bring about neural repair through various paracrine mechanisms. [36] BMMNCs secrete various neurotropic factors and anti-inflammatory cytokines including interleukin-10, insulin-like growth factor-1, vascular endothelial growth factor, and stromal cell-derived factor-1. [37] It causes neurogenesis, angiogenesis, reduction in the cell death and apoptotic process and enhances neuroplasticity which together lead to the

neurorestoration and improvements in the clinical outcomes. [38,39]

Clinical trials of autologous BMMNCs are found to be safe having no adverse effects. [6,16-19] No new complaints or neurological worsening were reported in our patient. It is widely believed that most stroke recovery occurs within 6 months, with little benefit of physiotherapy or other modalities beyond a year. This case report accentuates the effects of cellular therapy in chronic stroke. The voluntary control, memory, ambulation and the speech of the patient was found to be improved. The recovery was also marked by the change in the score of BBS and Beck depression inventory scale and the reach score. PET-CT brain imaging was used as the monitoring tool to study the effects of the intervention at the cellular level. Improvement in the metabolism was noted in PET CT scan report. These changes also correlated with the clinical improvements as shown in Table 2.

Table 2: Areas of brain showing improved metabolism and their clinical correlation

Areas of the brain showing increased metabolism	Functions improved
sensory motor cortex	voluntary movements and walking
posterior cingulate	memory
Cerebellum	posture, balance, coordination, and speech, resulting in smooth and balanced muscular activity

Limitation:

Though this is a single case study it highlights the fact that cellular therapy in addition to standard neurorehabilitation can achieve functional recovery even at the chronic stage of ischemic stroke.

CONCLUSION

The clinical improvements along with PET CT findings in this study suggest that autologous BMMNCs transplantation is safe, beneficial and has the potential of functional recovery in chronic ischemic stroke. It can be used in chronic stage of stroke along with standard treatment. PET CT can be used as a monitoring tool to record recovery after cellular therapy. However, to understand the efficacy of the cellular therapy in the chronic ischemic stroke further clinical trials in the form of multicentre randomized control studies are required.

Conflicts of Interest:

The authors declare that there is no conflict of interest regarding the publication of this article.

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