Stem Cell Therapy as a Treatment Modality for Neurotrauma

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Abstract

Neurotrauma is a common cause of chronic severe neurological deficits. No available treatment can reverse the neural damage. In recent advances, cell transplantation has emerged as a promising treatment modality to repair the damage. This is supported by numerous published animal studies. There have also been published human clinical trials which showed significant improvement in the neuro deficits. We have previously published three clinical studies and three case reports on the use of autologous bone marrow mononuclear cell (BMMNC) therapy in neurotrauma. Here we present a review of these studies which substantiate the use of cell therapy for neurotrauma. The clinical studies included a total of 179 cases of chronic neurotrauma which had 166 cases of spinal cord injury and 13 cases of traumatic brain injury. 146 out of 179 cases showed improvements after receiving cell therapy (82% cases improved) in combination with neurorehabilitation. These cases showed clinical improvements which were also recorded on objective scales. Functional neuroimaging performed before and after intervention has also shown improvements in the neural activity. No major adverse events were noted during any of these clinical studies. We conclude that the autologous bone marrow mononuclear cells in combination with rehabilitation is safe and feasible treatment strategy for chronic neurotraumatic conditions.

Keywords : *Neurotrauma, autologous, BMMNC, rehabilitation, spinal cord injury, traumatic brain injury*

Introduction

Neurotraumatic injuries are one of the leading causes of death and disability all over the world. It majorly involves the damage of the central nervous system which is made up of brain and spinal cord. The initial injury to the CNS is the primary damage which leads to a cascade of deleterious events known as secondary damage which further leads to loss of function and prolonged degeneration due to cell death. (1) This has devastating effects on quality of life of the affected individual. Hence, researchers are actively seeking a treatment strategy which can reverse as well as stop further damage caused to the CNS due to trauma or disease.

For a very long time, it was believed that damage to the CNS is irreversible. (2) However, growing research has shown that stem cells have the ability to restore the CNS. Stem cell therapy is emerging as a potential treatment strategy for conditions such as spinal cord injury, traumatic brain injury, brachial plexus, etc. (3,4) Effects of various types of cells such as embryonic stem cells, adult stem cells, umbilical cord blood cells and induced pluripotent stem cells have been actively studied in these disorders. (5,6) It is essential to select suitable cells to achieve optimal therapeutic efficacy. However, adult stem cells are the most preferred type of cells. The underlying mechanism of action of these cells is that they help in neuromodulation, neuroprotection, axon sprouting, neural circuit reconstruction, neurogenesis, neuroregeneration, neurorepair, and neuroreplacement. (7,8)

To demonstrate the therapeutic benefits of these cells in chronic neurotraumatic conditions, we administered 179 cases of chronic neurotrauma (spinal cord injury and traumatic brain injury) with autologous bone marrow mononuclear cells intrathecally. These cells are easily obtainable, do not involve any immunogenic complications and ethical issues. Here, we present a review of our previously published research data on the use of stem cell therapy as a treatment modality for neurotrauma.

Material and Method

Study Design

We performed a study to demonstrate the effect of intrathecal autologous bone marrow mononuclear cells in patients with chronic neurotraumatic conditions such as spinal cord injury and traumatic brain injury. This is a review of three case series and three case reports.

Intervention Protocol

The protocol of the study was reviewed and approved by The Institutional Committee for Stem Cell Research and Therapy (IC-SCRT) in accordance to the Indian Council of Medical Research (ICMR) guidelines. Patients were selected based on the World Medical Association Helsinki Declaration for Ethical Principles for medical research involving human subjects (9). A written informed consent was obtained from the patients and their families depending on the patient's cognitive status. The inclusion criteria were diagnosed cases of chronic neurotraumatic conditions and age above 1 year. The exclusion criteria were presence of acute infections such as HIV / HBV / HCV, malignancies, bleeding tendencies, renal failure, severe liver dysfunction, severe anemia [Hb < 8], pregnancy, lactation, any bone marrow disorder and other acute medical conditions such as respiratory infection and pyrexia.

Before the intervention, every patient underwent a detailed neuroevaluation by medical experts. Serological, biochemical and hematological tests were also performed. Functional independence of all the patients was evaluated using Functional Independence Measure (FIM). Electroencephalography (EEG), Electromyography (EMG), Nerve conduction velocity (NCV), Somatosensory evoked potentials (SSEP), Magnetic Resonance Imaging (MRI) of brain, with Diffusion tensor imaging (DTI), functional Magnetic Resonance Imaging (fMRI) of brain and Positron Emission Tomography- Computed Tomography (PET-CT) brain scans were performed in patients before the treatment depending on the disorder.

Bone marrow aspiration, separation and injection

Granulocyte Colony Stimulating Factor (G-CSF) injections were administered 48 hours and 24 hours prior to the procedure as it stimulates and mobilizes the bone marrow stem cells (10).

Approximately 80-100 ml bone marrow was aspirated from the anterior superior iliac crest under local anesthesia with or without mild sedation (depending on the case scenario), using the bone marrow aspiration needle. MNCs were separated using density gradient centrifugation method. Their viability is checked manually using trypan blue dye and confirmed with propidium iodide dye in TALI (Life Technologies. Invitrogen). Average viability was found to be 97%. CD34+ counting was also performed by fluorescence activated cell sorting (FACS) using CD34 PE antibody.

The separated autologous BMMNCs (body weight x 106) were immediately injected intrathecally using a 25G spinal needle between fourth and fifth lumbar vertebrae under local anesthesia with or without mild sedation (depending on the case scenario),. Simultaneously, 20mg / kg body weight methyl prednisolone in 500 ml Ringer Lactate was given intravenously to enhance survival of the injected cells.

Neurorehabilitation

The intervention included neurorehabilitation along with stem cell therapy. A multidisciplinary neurorehabilitation plan was customized for every case which included physiotherapy, occupational therapy, speech therapy and psychological intervention. The regime was commenced immediately after stem cell therapy and was advised to continue as a home program.

Patients were followed up regularly at 3 months,

6 months and yearly thereafter after the intervention. A complete neurological evaluation was performed.

Result

The 179 cases of chronic neurotrauma included 166 cases of spinal cord injury and 13 of traumatic brain injury . The average age of the study sample was 33 years.

Amongst the 166 cases of spinal cord injury, 110 cases were of dorsolumbar level while 56 were of cervical level. Overall, 100 out of 110 (91%) patients showed improvements. (Figure1) Improvement in trunk control was observed in 95.6% cases, bladder management in 33% with respect to shift from indwelling and condom catheter to self intermittent catheterization, partial sensory recovery in 27% and reduction of spasticity in 26%. All the patients showed improvement in postural hypotension. 38% wheelchair bound patients started walking with assistance. Functionally, 27% showed improved activities of daily living (ADLs) and 53.6% showed a positive change in FIM score. 10% cases showed a shift in ASIA scale. On electrophysiological studies, 2 showed improvement and 1 showed change in functional MRI.

However, in cervical SCI patients, 37 out of 50 (74%) showed improvements. (Figure 2) Sensation recovery was observed in 26% cases, improved trunk control in 22.4%, spasticity reduction in 20% and bladder sensation recovery in 14.2%. All the 50 cases had improvement in postural hypotension. 12.24% wheelchair bound patients started walking with assistance. Functionally, 20.4% patients showed improved ADLs and 48% showed a positive change in FIM score. 6% cases showed a shift in ASIA scale.

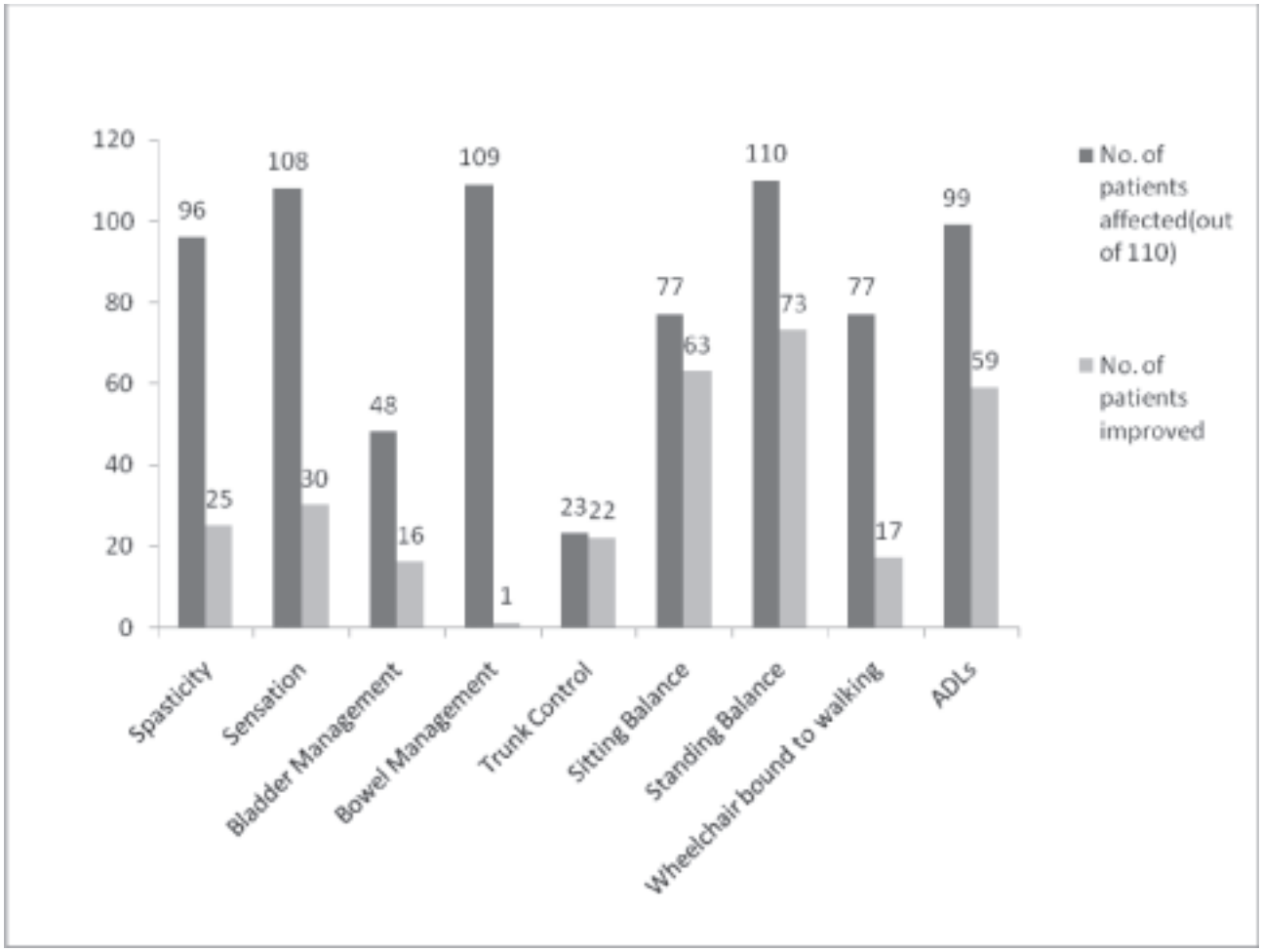

Figure 1: Graph representing symptomwise improvements in dorsolumbar spinal cord injury patients after stem cell therapy

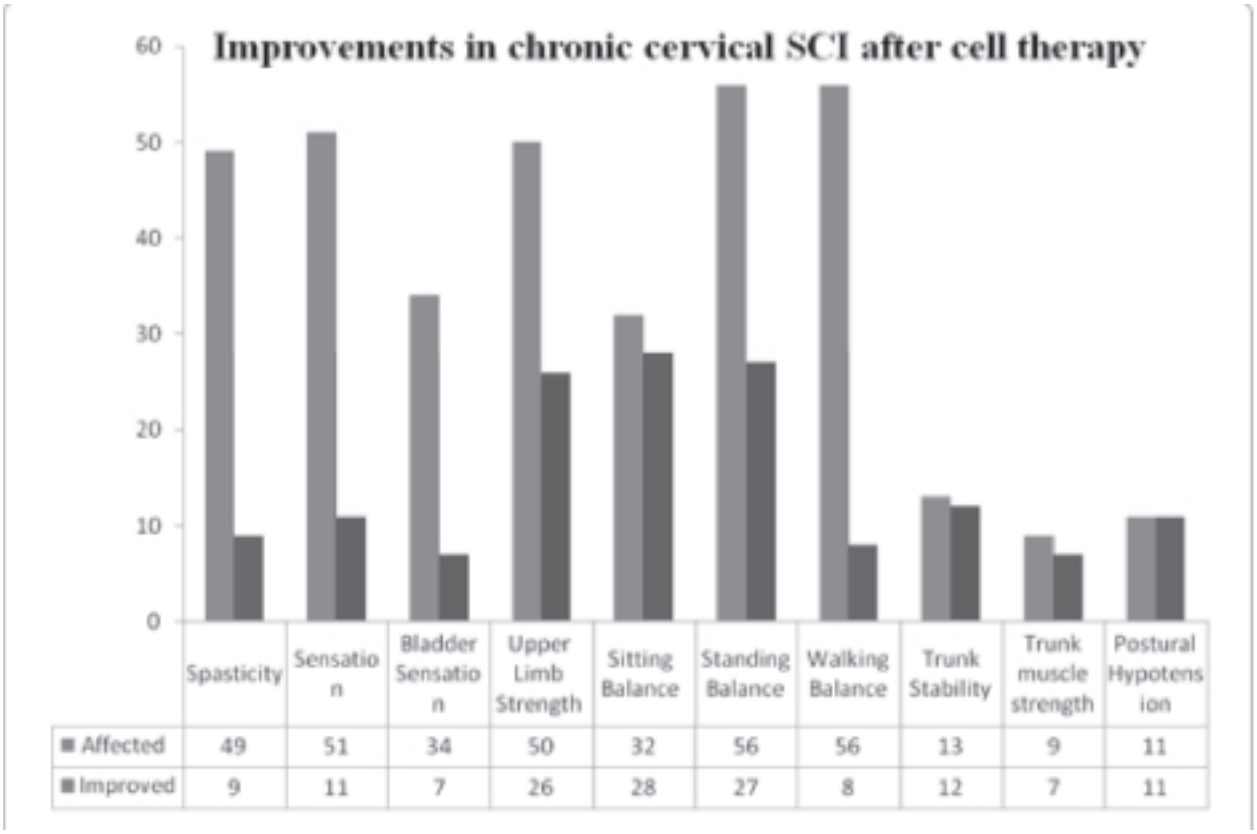

Figure 2: Graph representing symptomwise improvements in cervical spinal cord injury patients after stem cell therapy

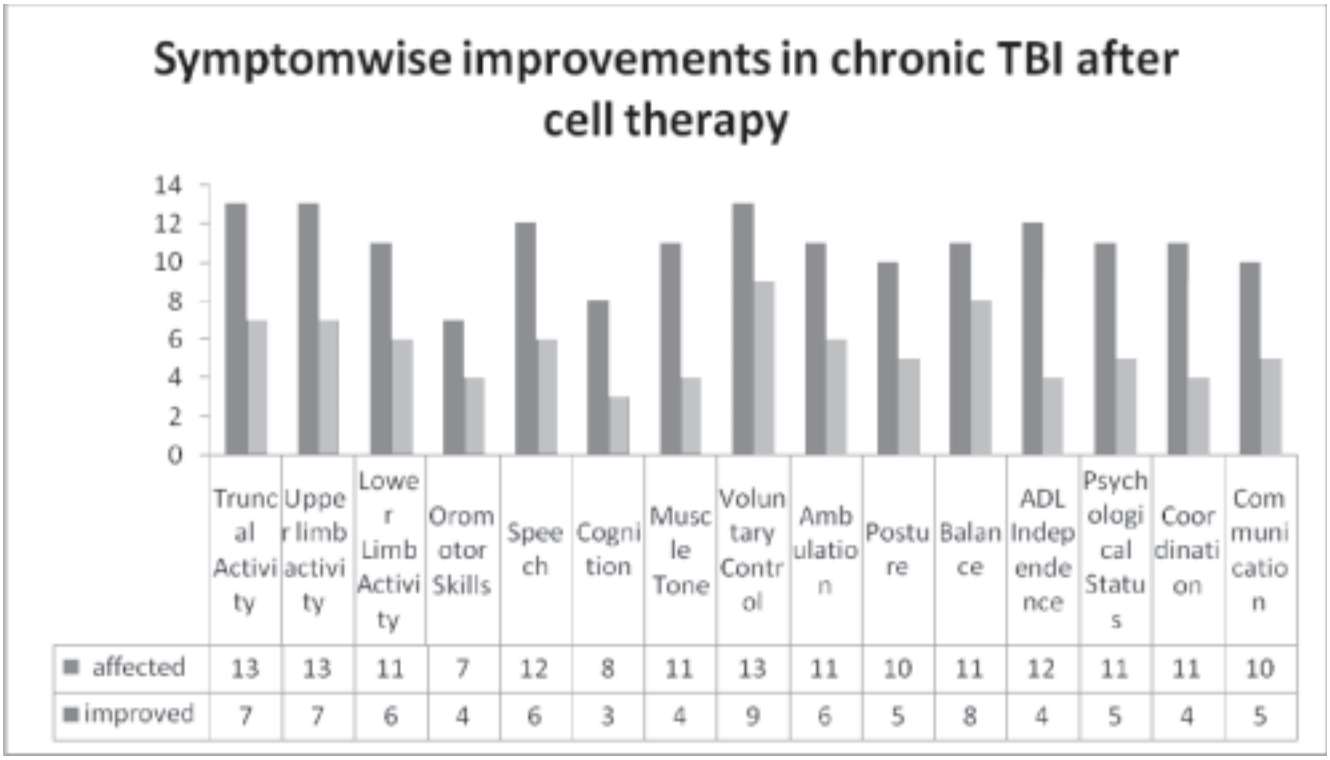

Figure 3: Graph representing symptomatic improvements in traumatic brain injury after cell therapy

In Traumatic Brain Injury, (Figure 3) amongst 13 patients, 73% showed improvement in balance, 69% in voluntary control, 60% in memory, 57% in oromotor activities, 55% in lower limb activity and ambulation and gait patterns, 54% in trunk and upper limb activity, 50% in speech, posture and communication, 45% in psychological status, 38% in cognition, 36% in muscle tone and coordination and 33% in ADLs. PET CT scan was repeated in 3 patients at the end of six months and they showed improved metabolism after intervention. The changes were consistent with the clinical and functional improvements demonstrated by these patients.

No major side effects were recorded in the duration of follow up. Minor procedure related side effects such as headache, nausea, vomiting, and backache were observed in a few cases which were controlled with medications.

Discussion

Neurotrauma is not only characterized by focal abnormalities but also multifocal, global structural and functional damage of the brain and spinal cord network. (11) The trauma results in loss of neuronal and oligodendroglial cells, reactive astrogliosis, and proliferation / activation of microglia. (12)Due to loss of functions, these conditions highly affect the quality of life of the injured patients. There are currently no treatments available to reverse the damage to the CNS.

Stem cell therapy has shown to be a potential treatment strategy for chronic neurotraumatic conditions. These cells either directly or indirectly help in reversal of the damage. These cells have anti-inflammatory, immunomodulatory and neuroprotective effects. (13,14) They have the ability to multiply and engraft diffusely to replace the lost cells of the CNS. They replace neurons and oligodendrocytes lost to necrosis or apoptosis and help to remyelinate axons. They also impart neuroprotective and neuroregenerative functions by releasing various growth factors. These growth factors stimulate the endogenous resident stem cells to multiply and replace the lost cells. These mechanisms might help in reconstructing the molecular and cellular milieu of the injured brain and spinal cord. (15,16)

We conducted an analysis on 179 cases of chronic neurotrauma to study the effect of autologous bone marrow mononuclear cells, administered intrathecally. These cells are a heterogeneous mixture of hematopoietic cells, mesenchymal cells, very small embryonic like cells (VSELs) and endothelial progenitor cells. (17) It has been observed that use of BMMNCs is more successful than the sub fractionated cell preparations. The cell mixture promotes angiogenesis and vascular repair. (18) These cells have the capacity to mobilize to the damaged areas and exert their reparative effects. We chose to administer the cells intrathecally as they are minimally invasive and are more targeted than intravenous transplantation. It has been observed that the cells administered intravenously get trapped in the lungs hence affecting the number of cells reaching the target tissue. (19) Direct injection to the site of the injury may be the most efficient route, but it involves an invasive procedure which could result in secondary damage.

All the patients included in the study underwent neurorehabilitation after stem cell therapy. It has been observed in animal studies that the combination of rehabilitation along with stem cell therapy results in a positive functional outcome.

On follow up, significant symptomatic improvement was observed in all the conditions. Improvement was also recorded on the outcome measures such as FIM and ASIA. Objective improvements were also observed in EMG, PET CT scan and fMRI of brain. These improvements in neurological functions indicate interaction between the microenvironment of the CNS and the implanted cells.

Conclusion

We conclude that the autologous bone marrow mononuclear cells in combination with rehabilitation is safe and feasible treatment strategy for chronic neurotraumatic conditions. The reparative effect of these cells is exhibited in the form of symptomatic, functional and objective improvements. However, to establish stem cell therapy as a standard treatment for these disorders, multicentre, large-scale, randomized clinical trials are required.

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