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■ CASE REPORT

Autologous Bone marrow Derived mononuclear cells for the treatment of Spinal Cord Injury.

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ABSTRACT

Spinal cord injury results in paralysis and loss of sensation below the level of injury. At present, there is no cure or effective treatment for spinal cord injury (SCI). Studies in SCI patients have shown that for a treatment to be effective it must primarily improve their quality of life. We report a case of incomplete spinal cord injury (L1-L2 compression fracture) with paraperesis, with approximately 6 months of follow-up who was administered bone marrow derived mononuclear cells (BMNCs) intrathecally. After the therapy, the patient had no side effects and underwent intensive neurorehabilitation. She showed some immediate improvements within a week and few improvements over a period of six months, which were quantified using Functional Independence Measure (FIM) and Manual Muscle Testing. The detailed case report is presented here with.

Keywords: Spinal cord injury, paraparesis, bone marrow, mononuclear cells.

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Introduction :

Spinal Cord Injury (SCI) may result due to traumatic incidents like vehicular accidents, sport injuries, violence or falls. (1) The presentation of SCI depends on the segments damaged and the degree of injury. A cervical spine injury results in quadriplegia whereas injury in thoracic or lumbar results in paraplegia. These further maybe either complete or incomplete injuries. Depending on the preservation of sensory and motor functions below the site of injury, (2) there can be extensive variability in the degree of preserved function after an incomplete SCI.The heterogeneity of SCI poses a challenge to the formulation of an effective standard of care.(3) Also, the recovery from central nervous system (CNS) injury is difficult due to the limited ability of the injured CNS to renew lost cells, restore disrupted myelin and re-establish functional neural connections.(4) Many treatments regimens have been under clinical trials in acute conditions such as use of methylprednisolone, (5) GM1 ganglioside, (6) decompression(7) and 4-aminopyridine. (8) All of these have shown minor benefits along with adverse side effects.(5-8) Autologous bone marrow stem cells have been deemed to be a viable & complementary option for treating SCI in emerging clinical studies primarily due to easy accessibility and absence of immunological reaction. Unlike embryonic stem cells, they are neither surrounded by any ethical issues or controversies surrounding them nor do they have tumorogenic potential. (9)

In view of these features, intrathecal autologous bone marrow transplantation is being assessed here for its safety and efficacy to further improve the quality of life of a patient with an incomplete spinal cord injury in combination with an intensive course of neurorehabilitation.

Materials and methods:

Patient selection was based on the inclusion criterion as per paragraph 32 of the World Medical Associations Helsinki declaration. (10) The protocol had been reviewed and approved by the Institutional committee for Stem cell Research and Therapy (IC-SCRT). A duly filled informed consent was obtained from the patient and her relatives. Routine pre operative blood tests, MRI Lumbo Sacral spine, SSEP were

performed before the transplantation. G-CSF (300 mcg) injections were administrated subcutaneously, 48 hours and 24 hours prior to the bone marrow aspiration. The patient also underwent extensive neurological examination and was assessed on the basis of ASIA (American Spinal Injury Association) scale and FIM (Functional Independence Measure) scale.

Bone marrow (100ml) was aspirated from the iliac bone under local anesthesia using a standard procedure. Mono Nuclear Cells (MNCs) were obtained using the density gradient separation method. The purified MNCs were tested for total cell count, viability and CD 34+ cell content by FACS analysis. Viable count was found to be 98% and CD34+ percentage was found to be 0.47%. Approximately $65x10^6$ MNCs were immediately injected intrathecally in L3-L4 space using a epidural set and catheter. (11) 1gm (Solumedrol) methylprednisolone was administered intravenously during the injection. The patient underwent intensive neurorehabilitation which included physiotherapy and occupational therapy. Rehabilitation interventions seek to promote recovery & independence through neurofacilitation. The signs and symptoms of spinal cord injury (SCI) significantly impact everyday activities. Occupational therapy plays an important role in the rehabilitation and management of SCI at all levels. An important therapeutic goal is to assist the patients to restore function, enabling them to participate in the activities and tasks that are important to them. The ability to participate in meaningful, everyday activities is essential to an individual's health and well-being.

Case report

A 35 year old female who had sustained a L1-L2 compression fracture following a vehicular accident in 2009 and had undergone a decompression and stabilization surgery with pedicle screw fixation immediately thereafter, was considered for autologus stem cell therapy at our centre. The duration of injury was 12 months, during which period, the patient had been rehabilitated optimally to an extent that she could maintain sitting at the edge of the cot when made to do so. She had developed partial bladder control wherein she could appreciate urine sensation and could void voluntarily with increased intra abdominal pressure (Crede's maneuver).

On admission for stem cell therapy, she was evaluated where in neurologically, she showed sensory loss below L2 level and had grade 3 muscle power in bilateral lower extremities proximally (in L1- L2 myotomes), with bilateral foot drop. She had Grade 5 muscle power in the left upper extremity and right upper extremity could not be assessed as she had multiple fractures of right upper arm and forearm which were stabilized with an external fixator. Functionally, she was dependent for all her activities of daily living (ADL) and was wheel chair bound for mobility.

On ASIA scale, her score was 'B' and on FIM scale she scored 53 with limitation in activities of self care, sphincter control, transfer and locomotion.

On investigations, MRI of her lumbosacral spine showed gliosis in the conus medullaris and anterior wedging of D5 vertebra along with compression fracture of the L1 vertebral body. Electrophysiological study displayed axonal motor neuropathy, involving lower limbs and bilateral S1 radiculopathy.

After the stem cell therapy, the patient had no side effects and her clinical course after the transplantation was uneventful. She underwent intensive neurorehabilitation which was continued thereafter for a period of 6 months. She was evaluated at regular time intervals, wherein she continued to show neurological and functional recovery over a period of time.

After the transplantation, improvements were noticed in her trunk mobility as well as mat activities, such as, rolling, sitting up from lying position, shifting on the edge of the bed and bridging activities. She could also transfer herself at the same level, viz, from the bed to wheelchair and back. She was also able to ambulate with minimum support on parallel bars thereby registering an improvement in her FIM scores from 53 to 66. On manual muscle testing her hip muscle power increased from Grade 2- to Grade 2+ bilaterally.

Over a period of six months, her hip and knee musculature strength improved further, mainly hamstrings from Grade 3 to Grade 3++ bilaterally, such that she was able to walk with bilateral ankle foot orthosis in the form of high boots with posterior steel shank without showing hyperextension of knee. She was also able to climb stairs with railing and one hand support. As she underwent continuous rehabilitation she showed significant improvements in her daily

activities like dressing independently, bed mobility, and transfers, climbing stairs. This further showed improvement in her FIM scores to 97.

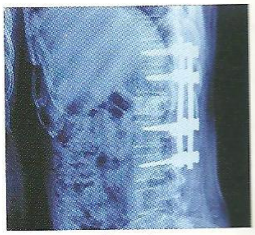

Figure 1
X Ray of the Lumbar spine (lateral view) with fixation in-situ

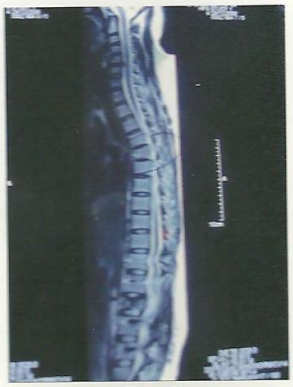

Figure 2
MRI Of Lumbosacral Spine Showing Gliosis in the conus medullaris and old compression fracture of the L1 vertebral body with anterior wedging of D5 vertebra.

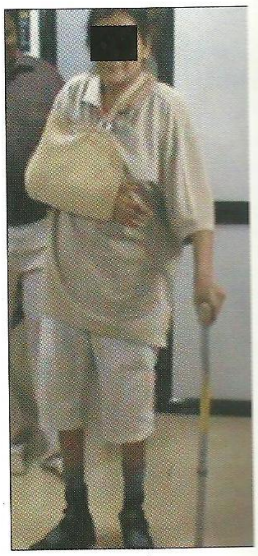

Figure 3
Post stem cell therapy improvement showing patient walking with a walking stick

Figure 4
Post stem cell therapy improvement showing patient climbing stairs with minimal support

Discussion :

Spinal cord injury leads to devastating dysfunction and disability afflicting millions across the world. It often results in severe and irreversible neurological damage. (13) SCI results in cell death, particularly in neurons, oligodendrocytes, astrocytes, and precursor cells. (14) Primary spinal cord injury results from the disruption of the cord structure at the time of injury while secondary injury is the additional damage occurring at a later stage around the primary injury. Studies have revealed that the site of spinal cord injury is typically replaced with a dense glial scar, providing a mechanical barrier against regenerative processes. (15) Complete recovery of a spinal cord injury till recent times has not been documented. People who survive a spinal cord injury will most likely have medical complications such as chronic pain along with an increased susceptibility to respiratory and heart problems. Bladder as well as bowel dysfunction is a common feature following a spinal cord injury. These are usually in the form of a neurogenic bladder, manifesting as either incontinence or retention. In either case, these patients have to resort to either a continuous indwelling catheter or if appropriately rehabilitated, may get away with intermittent catheterization. Spasticity and neuropathic pain are also additional common problems following a spinal cord injury, which need to be addressed with appropriate medical treatment. Many a times, intractable neuropathic pain and spasticity may become a hindrance to proper rehabilitation. However, some amount of spasticity, in fact is desirable for mobility, referred to as 'spasticity assisted' walking. Successful recovery depends upon how well these chronic conditions are handled day to day. (4)

High dose methylprednisolone and/ or decompression are presently the standard of care for acute SCI.(6) The mode of action of the steroids and other drugs is to suppress the messenger cascade triggered by SCI and thereby limit gliosis. Gliosis restricts the axons to regenerate and reestablish communications. (15, 16) However, they have not shown significant benefits and also come with side effects.

Autologous bone marrow derived mono nuclear cell (BMNC) transplantation represents a promising mode of therapy for SCI. Studies for the same have also been carried out. (17,18) Park et al have presented one of the earliest reports of intrathecal autologous bone marrow cell transplantation. Changes on MRI and ASIA scale were recorded along with sensory and motor recovery between 3 weeks and 7 months. (19). These cells comprise of a variety of cells like hematopoietic stem cells, tissue specific progenitor cells, stromal cells and specialized blood cells in different stages of development.

Based on these studies, autologous BMNC transplantation was carried out on a case of incomplete

spinal cord injury (L1-L2 compression fracture) with paraperesis. Significant improvements were recorded which included improvements in muscle strength and functional activities which further improved the quality of life to a great extent. Further clinical trials are required to establish the treatment.

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