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Promise of Autologous Bone Marrow Stem Cell Transplantation to Patients with Spinal Cord Injury-Current Status

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Abstract: Due to rapid industrialization, population raise and development of real estate business results to build of enormous constructions, which leads to the injuries of spinal cord. The burden of spinal cord injury induced limb paralysis increasing every year in India. Increasing vehicular traffic has caused numerous road traffic accidents. Spinal cord injury (SCI) affects all aspects of a patient's life, including the physical, behavioral, psychological and social functioning. [1] Spinal cord injuries could not be treated effectively with the existing treatment modalities. In view of the above, there is definitely an urgent need for finding different methods of treatment for these patients who cannot undergo established modalities of treatment or these have been tried unsuccessfully. Since a large number of these patients will loose their productive life and at the prime of their lives one such alternate therapy, which seems to offer some promise, is "stem cell" therapy, which has been well studied and published in prestigious journals. Current review discuss the safety and therapeutic efficacy of autologous human bone marrow cell (BMC) transplantation and the administration of granulocyte macrophage-colony stimulating factor (GM-CSF).

Keywords: Bone Marrow Stem Cell, American Spinal Injury Association Scale, Granulocyte Macrophage-Colony Stimulating Factor

1. Introduction

Spinal cord injury is an acute traumatic injury to the spinal cord that leads to varying degrees of motor and/or sensory deficits and paralysis. [2] Although injury of the cauda equina is included, the definition excludes isolated injuries to other nerve roots. [3] The condition can lead to life-long loss of function and reduced quality of life, as well as increased morbidity and mortality. In most countries, traffic accidents are the most common causes of SCI. [4-8] In India, various causes of SCI includes road traffic accidents, fall from trees, buildings or at the construction sites, railway accidents, sports injuries, gunshot wounds, etc. Upon these falling from height including roof, trees, electricity pole (44.5%) followed by motor vehicle accidents (34.7%). (Figure 1) The European-International Spinal Cord Society (ISCoS) and its American counterpart (the American Spinal Injury Association ASIA) have together developed an international data set for the registration of spinal cord injuries. In the National Spinal Cord Injury Statistical Centre Database (US), the average age at the time of injury was 29 years in 1970 and 37 years in 2005. [9] Whereas the risk of traumatic spinal cord injury is 2.5 times higher in rural than in urban areas. [10] In India (Kashmir)] Prevalence is 236 per million populations. [11] Approximate 20,000 new cases of SCI are added every year. 60-70% of them are illiterate, poor villagers. Most of them sustain this injury by fall from unprotected roofs, trees or fall into uncovered wells, which infact are preventable causes. [12] Fall from height was most common cause of trauma (44.5%), followed by motor vehicle accidents (34.7%).

Male to female ratio was 2.96:1 and the average age at injury was 35.4 years.

Figure 1. *Modes of Injuries.*

A spinal cord injury usually begins with a sudden, traumatic blow to the spine that fractures or dislocates vertebrae. The damage begins at the moment of injury when displaced bone fragments disc material, or ligaments bruise or tear into spinal cord tissue. Axons are cut off or damaged beyond repair, and neural cell membranes will be broken. Blood vessels may rupture and cause heavy bleeding in the central grey matter, which can spread to other areas of the spinal cord over the next few hours. Within minutes, the spinal cord swells to fill the entire cavity of the spinal canal at the injury level. This swelling cuts off blood flow, which also cuts off oxygen to spinal cord tissue. Blood pressure drops, sometimes dramatically, as the body loses its ability to self-regulate. As blood pressure lowers even further, it interferes with the electrical activity of neurons and axons. All these changes can cause a condition known as *spinal Shock* that can last several hours to several days. During spinal shock, even undamaged portions of the spinal cord become temporarily disabled and can't communicate normally with the brain.

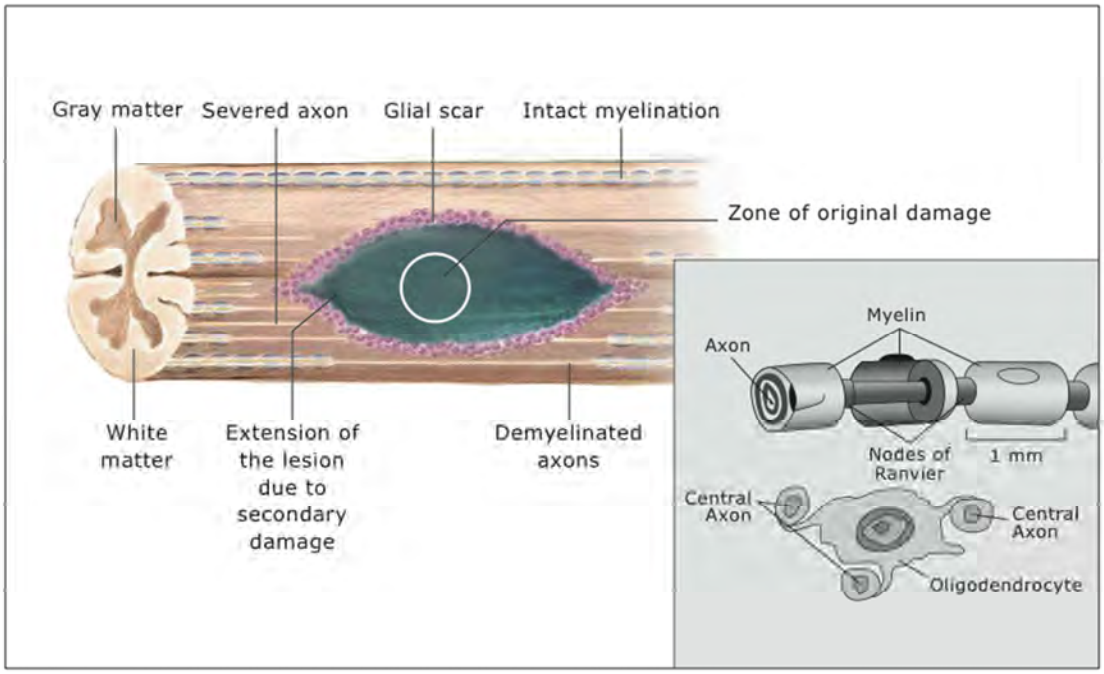

Figure 2. *Mechanism of disease.*

The crushing and tearing of axons is just the beginning of the devastation that occurs in the injured spinal cord and continues for days. The initial physical trauma sets off a cascade of biochemical and a cellular event that kills neurons, strips axons of their myelin insulation, and triggers an Inflammatory immune system response days or a sometimes even week later, after this second wave of damage has passed, the area of destruction has increased sometimes to several segments above and below the original injury and so has the extent of disability (Figure 2). Excessive release of neurotransmitters kills nerve cells An invasion of immune system cells creates inflammation. Free radicals attack nerve cells and nerve cells will self destruct. The anatomical level of injury in the spinal cord is divided into high (cervical) and

low injuries (thoracic, lumbar and sacral). [13] The neurological level of injury is defined as the most caudal segment of the spinal cord that has normal function. In 10 - 15% of the patients with traumatic spinal cord injury there is a difference between the anatomical and the neurological levels of injury because of multi-level injuries, vascular pathologies and/or a spinal-cord oedema following from the injury. [14] The neurological level of injury is classified according to the American Spinal Injury Association (ASIA) Impairment Scale A-E. [15] The symptoms of the patient range from mild local site pain to quadriplegia and death. If the injury is at the level of the cervical spine, it may lead to quadriplegia, and if the impact is below the level of dorsal or lumbar, then it may lead to paraplegia. Functional deficits following SCI result from damage to or severance of axons, loss of neurons and glia, and demyelination. SCI pathology is determined not only by the initial mechanical insult, but also by secondary processes including ischemia, anoxia, free-radical formation, and excitotoxicity that occur over hours and days following injury. In the Western world, lethality from traumatic spinal cord injury in the acute phase declined from 30% in the 1960s to 6% in the 1980s. [16, 17] Previously, urosepsis was the most common cause of death after a traumatic spinal cord injury, [18] while today the most common causes include respiratory problems, heart disease and suicide. [19] Pneumonia is the most common cause of death among patients with cervical spinal cord injuries and patients over 60 years. [20] Suicide is a frequent cause of death among patients with thoracic, lumbar and sacral injuries. [21]

Methylprednisolone, a steroid drug, became standard treatment for acute spinal cord injury in 1990 when a large scale clinical trial supported by the National Institute of Neurological disorders and stroke showed significantly better recovery in patients who were given the drug within the first 8 hours after injury. Methylprednisolone appears to reduce damage to nerve cells and decreases inflammation near the injury site by suppressing activities of immune cells. Realignment of the spine using a rigid brace or axial traction is usually done as soon as possible to stabilize the spine and prevent additional damage.

Stimulating the regeneration of axons is a key component of spinal cord repair because every axon in the injured spinal cord that can be reconnected increases the chances for recovery of function. Research on many fronts reveals that getting axons to grow after injury is a complicated task. CNS neurons have the capacity to regenerate, but the environment in the adult spinal cord does not encourage growth. Not only does it lack the growth-promoting molecules that are present in the developing CNS, it also contains substances that actively inhibits axon extension. For axon regeneration to be successful, the environment has to be changed to turn off the inhibitors and turn on the promoters. Investigators are looking for ways to take advantage of the chemicals that drive or halt axon growth: growth-promoting and growth-inhibiting substances, neurotrophic factors, and guidance molecules.

At least three growth-inhibitory proteins operating within the axonal tract have been identified. the task of researchers is to understand how these inhibitory proteins do their job, and then discover ways to remove or block them, or change how the growth cone respond to them. Growth-inhibiting proteins also block the glial scar near the injury site. To get past, an axon has to advance between the tangles or long, branching molecules that form the extracellular matrix. A recent experiment successfully used a bacterial enzyme to clear away this underbrush so that axons could grow. A treatment that combines both these approaches-turning off growth-inhibiting proteins and using enzymes to clear the way-could create an encouraging environment for axon regeneration. But before trails of such a treatment can be attempted in a patient, researches must be sure that it could be controlled well enough to prevent to prevent dangerous miswiring of regenerating axons. Neurotrophic factors (or neurotrophins) are key nervous system regulatory proteins that prime cell to produce the molecule machinery necessary for growth. Some prevent oligodendrocyte death, others promote axon regrowth and survival, and still others serve multiple functions. Unfortunately, the natural production of neutrophins in the spinal cords falls instead of rising during the weeks after injury. Researchers have tested whether artificially rising the levels post-injury can chance regeneration. Some of these investigations have been successful. Infusion pumps and gene therapy techniques have been used to deliver growth factors to injured neurons, built they appear to encourage sprouting more than they stimulate regeneration for long distances. Axonal growth isn't enough for functional recovery. Axons have to make the proper connections and re-establish functioning synapses, guidance molecules, proteins that rest on or are released from the surfaces of neurons or glia, act as a chemical road signs. Beckoning axons to grow in some directions and repelling growth in others.

Supplying a particular combination of guidance molecules or administering compounds that induce surving cells to produce or use guidance molecules might encourage regeneration. But at the moment, researchers don't understand enough about guidance molecules to know which to supply and when. Researchers hope that combining these strategies to encourage growth, clear away debris, and target axon connections could reconnect the spinal cord. Of course, all these therapies would have to be provided in the right amounts, in the right places, and at the right times. As researchers learn more and understand more about the intricacies of axon growth and regeneration, combining therapies could become a powerful treatment for spinal cord injury.

Central nervous system (CNS) axonal regeneration appears to be impede partly by myelin-associated inhibitors [22], loss in adult neurons of an intrinsic ability to overcome inhibitory cues, [23] and formation of a post-lesion scar barrier. [24] However, if axons can traverse the injury site, there is evidence that they may regrow in unscarred regions. [25, 26] Furthermore, preservation of even a small percentage of

tissue significantly enhances functional recovery. [27] Although there have been encouraging reports of deficit reduction [28-30] and axonal regrowth by blocking inhibitory molecules and antagonizing secondary injury mechanisms [31]; myelin replacement by stem [32], Schwann, and olfactory ensheathing cells [33, 34]; delivery of growth factors and small molecules [35-37]; and implantation of fetal tissue [38] and scaffolds [39, 40], as yet there is no practical treatment for SCI.

2. Recent Advances in SCI Treatment

Recovery in central nervous system disorders is hindered by the limited ability of the vertebrate central nervous system to regenerate lost cells, replace damaged myelin, and re-establish functional neural connections. There has been successful research in a number of fields that may someday help people with spinal cord injuries. Genetic studies have revealed a number of molecules that encourage axon growth in the developing CNS but prevent it in the adult. Basic research has helped describe the mechanisms involved in the mysterious process of apoptosis, in which large groups of seemingly healthy cells self-destruct. New rehabilitation therapies that retain neural circuits through forced motion and electrical stimulation of muscle group are helping injured patients regain lost function. Researchers, many of whom are supported by the National Institute of Neurological Disorder and Stroke (NINDS), are focused on advancing our understanding of the key principles of spinal cord repair:

a. Protecting surving nerve cells from further damage.
b. Replacing damaged nerve cells stimulating the regrowth of axons and targeting their connections appropriately.
c. Retraining neural circuits to restore body function

Cell transplantation to repair central nervous system disorders is an active area of research, with the goal of reducing functional deficits. Several types of cells have been studied for their potential to promote regeneration and repair, including Schwann cells, olfactory unsheathing glia, fetal spinal cord cells, and embryonic stem cells. Recent animal studies showed that cells of the hematopoietic stem cell (HSC) fraction of bone marrow transdifferentiated into various nonhematopoietic cell lineages. In these studies they demonstrated a significant improvement in the functional outcome of mice transplanted with hematopoietic stem cells compared with control mice in which only medium was injected. Fluorescent in situ hybridization for the Y chromosome and double immunohistochemistry showed that transplanted cells survived 5 weeks after transplantation and expressed specific markers for astrocytes, oligodendrocytes, and neural precursors, but not for neurons. [41]

In another study by Snyder et al., 1997 demonstrated that intracerebral transplantation of cells may promote neurogenesis. [42] Intrastriatal fetal graft has been used to reconstruct damaged basal ganglia circuits and to ameliorate behavioral deficits in a mammalian model of ischemia. [43] Fetal hematopoietic stem cells (HSCs) transplanted into the adult organism or adult HSCs transplanted into an embryo results in a chimera that reflects the endogenous cells within the microenvironment into which the cells were seeded (44). Pluripotent stem cells are harbored in the adult CNS and the adult brain can form new neurons. [45, 46]

3. Bone Marrow Mesenchymal Stem Cells for SCI

Bone marrow cells are a mixed cell population including hematopoietic stem cells, mesenchymal stem cells, endothelial progenitor cells, macrophage, and lymphocytes. It has been shown in other studies that hematopoietic or mesenchymal stem cells had a neuroprotective effect and increased neurite outgrowth. [47] Furthermore, activated macrophages are currently being investigated as a therapeutic target for SCI patients. [48, 49] In contrast, inflammatory cells in BMCs could have adverse effects, such as increasing the inflammatory response, thus inhibiting the regeneration process. [50, 51, 54, 55] As a result, further studies comparing the effects of whole BMCs with those of a subpopulation with inflammatory cells removed are required. Bone marrow stem cells contains at least two types of stem cells, hematopoietic stem cells and stem cells of non-hematopoietic tissues variously referred to as mesenchymal stem cells or bone marrow stromal cells (BMSCs). MSC are also referred to as mesenchymal stem cells because they are capable of differentiating into multiple mesodermal tissues, including bone, cartilage fat and muscle. [51-54] In addition, differentiation into neuron-like cellsexpressing neuronal markers has been reported, [55, 56] suggesting that MSC may be capable of overcoming germ layer commitment. MSCs are of interest because they are easily isolated from a small aspirate of bone marrow and they readily generate single cell derived colonies. The single-cell derived colonies can be expanded through as many as 50 population doublings in about 10 weeks, and can differentiate into osteoblasts, adipocytes, chondrocytes [51, 53, 57], myocytes [58], astrocytes, oligodendrocytes, and neurons. [54, 59-61] For these reasons, MSCs are currently being tested for their potential use in cell and gene therapy of a number of human diseases. [62]

MSCs constitute an alternative source of pluripotent stem cells. Under physiological conditions they maintain the architecture of bone marrow and regulate hematopoiesis with the help of different cell adhesion molecules and the secretion of cytokines, respectively. [63] MSCs grown out of bone marrow by their selective attachment to tissue culture plastic can be efficiently expanded [60] and genetically manipulated. [34] Azizi et al. transplanted human bone marrow stromal cells (hBMSCs) into the brains of albino rats. [60] Their primary observations were that hBMSCs can engraft, migrate and survive in a manner similar to rat astrocytes. Further, it has been demonstrated that the bone marrow cells when implanted into the brain of adult mice can differentiate into microglia and macroglia. [64] Again, this occurred when the bone marrow cells were transplanted into

the brain of normal mice. There have been many attempts made to use bone marrow stromal cells in cell therapy in an animal model. However, there has been little evidence of using bone marrow mesenchymal stem cells in a diseased animal model or otherwise an animal that is suffering from a disease. Thus, there is a long felt need in the art for efficient and directed means of treating a neurodegenerative disease such as Spinal cord injury in humans.

It has long been believed that intrinsic repair is quite restricted after spinal cord injury (SCI) because neurogenesis rarely occurs in the central nervous system (CNS). As a result, cell transplantation has become a promising therapeutic option for SCI patients. Many experimental studies have suggested that the transplantation of bone marrow cells (BMCs), neural progenitor cells, or olfactory ensheathing cells could promote functional improvements after SCI. [64-66, 75-78] In recent years, some have found that BMCs differentiate into mature neurons or glial cells under specific experimental conditions. [55, 67] These findings imply the therapeutic potential of BMCs in patients with neurological diseases and can obviate ethical problems.

The grafting of BMCs into the SCI models has been actively studied. Transplanted BMCs were found to improve neurological deficits in the CNS injury models by generating neural cells or myelin producing cells. [60, 68] Furthermore, BMCs can produce neuroprotective cytokines, which rescue the neurons with impending cell death after injury. [69, 70] Several clinical trials have explored the hypothesis that cell transplantation may enhance the recovery of neurologic functions after SCI. However, it was reported that significant functional recovery after cell transplantation was rarely achieved in the human clinical trials. [71, 72] These reports raise a concern that treatment protocols using only cell transplantation are not sufficient to achieve the required therapeutic goals in SCI.

Recently, it has been reported that hematopoietic cytokines including granulocyte macrophage-colony stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF), or erythropoietin had neuroprotective effects and improved neurologic functions after CNS injury. [72-76, 88-92] These findings suggest that GM-CSF, which is popularly used and considered safe for hematologic disease, could be used for SCI treatment. Ha Y et al 2005 study reported that GM-CSF decreased neuronal apoptosis and improved the functional outcome in SCI animal models. Furthermore, it has been published that GM-CSF stimulates microglial cells to increase brain-derived neurotrophic factor (BDNF) synthesis. [76] As a result, it was hypothesized that administration of GM-CSF to SCI patients could be an adjunct measure to improve the therapeutic effects of BMC transplantation.

4. Experimental & Clinical Studies

Many experimental studies have been completed to find the optimal period for cell transplantation. To avoid the destruction of transplanted cells by the inflammatory process in the acute phase (less than 1 week), many researchers consider the subacute phase between 10 and 14 days as an optimal period for cell transplantation. Results from animal studies show that significant gliosis is a major obstacle inhibiting axonal regeneration during the chronic stage. [77, 78] Interestingly, few patients in previous study showed neurologic improvement even if BMC transplantation was performed between 2 and 8 weeks after injury. These results indicate that the optimal period of BMC transplantation in SCI patients should not be restricted to patients less than 2 weeks post injury.

Few studies have been published that identify cell transplantation therapy as an ideal option for improving the neurologic functions in patients at the chronic stage. These previous study findings imply that autologous BMC transplantation doesn't increase the risk of malignant transformation, which is still a field under investigation in adult stem cell transplantation.

The use of autologous BMCs for stem cell therapy in SCI patients has more advantages. First, one can avoid all problems associated with the immunological rejection or graft-versus-host reactions [96], which are frequently caused in allogenic cell transplantation. Second, autologous BMC therapy is considered safe by not being associated with carcinogenesis. [79] Third, extensive scientific data on BMCs have been accumulated from previous experiences in BMC transplantation for hematological diseases. These advantages have made cell therapy using BMCs widely applicable and investigated clinically in various neurologic diseases. However, it also has some disadvantages. First, the procedure requires open surgery to approach the injury area, which results in the increase in the potential adverse effects. Second, the sorting of BMCs needs to be done *in vitro*, thus increasing the risk of contamination. Third, it is still unclear whether some BMC components may have a deleterious effect on the functional improvement.

Recombinant human GM-CSF has long been used safely in patients with bone marrow suppression. It is well known that the classic role of GM-CSF is hematopoiesis by inducing the growth of several different hematopoietic cell lineages. It also enhances the functional activities of mature effector cells involved in antigen presentation and cell-mediated immunity, including neutrophils, monocytes, macrophages, and dendritic cells. Recently, some studies have reported that GM-CSF prevented apoptotic cell death not only in hematologic cells but also in neuronal cells [80, 81]. From these findings, it was speculated that administration of GM-CSF to SCI patients would result in the improvement of neurologic functions without any significant complication. In this study, a hypothesis was developed that GM-CSF would not only activate patient bone marrow for stem cell mobilization but would also have a direct effect on the transplanted BMCs by enhancing their survival in the spinal cord and activating them to excrete neurotrophic cytokines. Recently, some investigators found that GM-CSF stimulated microglial cells to produce neurotrophic cytokines such as BDNF. [76] Furthermore, other hematopoietic cytokines

including G-CSF and erythropoietins were also shown to have neuroprotective effects and promote neurologic outcomes in CNS injury models. [73, 74] Since the safety of most hematopoietic cytokines is already verified in the clinical fields, these experimental studies could be rapidly turned into clinical investigation. Previous findings imply that patients who are more responsive to GM-CSF might have a greater capacity for improvement. However, it is not clear at this point that the higher level of leukocytosis is a prerequisite for the GM-CSF effect and/or the recovery from SCI.

5. Status of Stem Cell Clinical Research

Various studies have been demonstrated the application of the infusion of neural precursors derived from bone marrow followed GMCSF injection and physical rehabilitation post operative. Transplantation of bone marrow cells into the injured spinal cord has been found to improve neurologic functions in experimental animal studies. The majority of hematopoietic stem cells (HSCs), and mesenchymal stem cells transplantations in animal models of SCI occur in the acute injury phase. [77, 78, 82-85] However, there are a number of studies using chronic models of SCI in animals that have reported increased functional recovery following MSC transplantation 6-12 weeks after injuries were induced, which is considered chronic in these model systems. [86, 87]

Mononuclear cells preparations (MCPs) have been trialed in conjunction with granulocyte-macrophage colony-stimulating factor (GM-CSF) administration. GM-CSF has previously been shown to mobilize MCPs into the injured spinal cord and promote functional recovery from SCI in mice. [88] The first trial used a combination of MCPs with administration of GM-CSF in the acute setting, that is, within 7 days of injury with cells injected directly into the lesion site. Of the 6 patients who were treated, 5 showed slightly improved neurological function. [89] A preliminary safety study on the use of MCPs delivered via lumbar puncture with administration of GM-CSF for the treatment of SCI has been reported. [89] Another trial safely treated patients with SCI ranging from 10 to 467 days post injury with MCPs injected intra-arterially or by IV. [90, 91] The improved neurological outcome reported in these chronic patients is exciting, although a control group was again not included in either study for comparison. [92, 93] (Figure 3) (Figure 4)

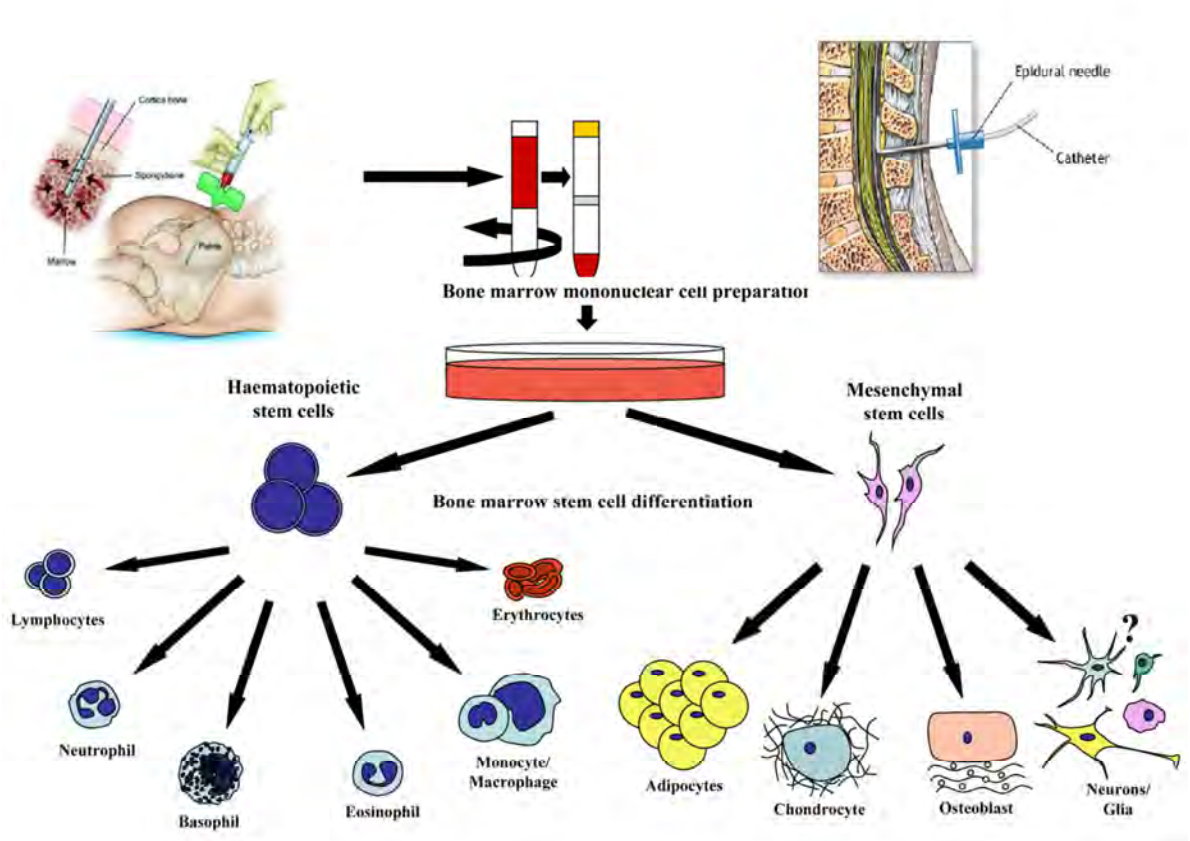

Figure 3. *Bone marrow aspiration and in vitro cell differentiation.*

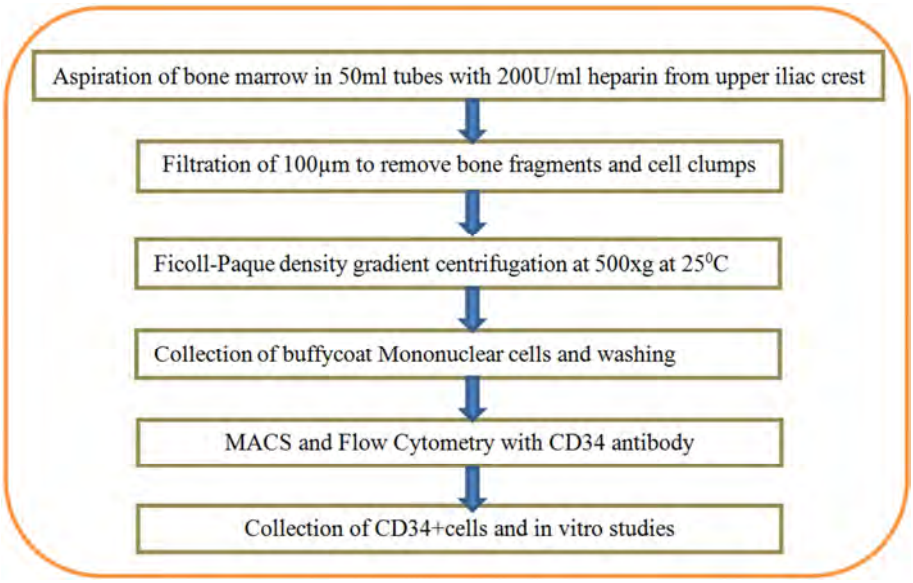

Figure 4. *Procedure of Human Bone Marrow Cell isolation and in vitro studies.*

In acute SCI patients, transplantation will be done within 14 days after admission. Neurologic examination will be performed immediately before operation to confirm complete SCI. Complete laminectomy will be performed from one vertebra above to one below in order to provide sufficient access to the transplantation site. The dura mater will be incised, sparing the arachnoid, which was subsequently opened separately with microscissors. The dorsal surface of the contusion site will be located using high-power microscopic magnification.

After exposure of sufficient surface at the contusion site, 300-µl aliquots of cell suspension (total volume of 1.8 ml) will be injected into five or six separate positions surrounding the lesion site with the injection depth of 5 mm from the dorsal surface and 5 mm lateral from the midline.

To avoid mechanical injury during injection, 2×10^8 cells will be injected at a rate of 300 µl/minute using a 21-gauge needle attached to a 1-ml syringe. To prevent cell leakage through the injection track, the injection needle will be left in position for 5 minutes more after completing the injection. The dura mater and arachnoid will be closed. The muscle and skin will be closed layer by layer.

Patient will be discharged from Hospital after first physiotherapy.

[Note: the time required for the discharge will be change from patient to patient based on primary recovery.]

GM-CSF Injection Schedule

After surgery, a total of five cycles (daily for the first 5 days of each month over 5 months) of GM-CSF will be injected subcutaneously (250 g/m^2 of body surface area). During the GM-CSF administration, vital signs will be checked and complete blood analysis will be taken daily.

Each Visit: the following tests will be done at each visit

Neurological assessment, MRI, Evoked potentials and Urodynamics. During all follow up visits a routine physical examination and evaluation of clinical signs and symptoms will be done. A detail examination will be done to exclude the presence of any signs and symptoms of secondary infection and will be documented in the source records. The laboratory investigations to be done during the follow up visits are outlined in the schedule of events.

Long term follow up: All patients will be counseled about life style modification, structured exercise program and appropriate limb care.

Efficacy assessment: Primary efficacy outcome will be significant clinical improvement in ASIA impairment 6 points of ASIA motor score or improvement by at least one grade and general condition.

Changes in ASIA sensory scores, Spinal cord injury measure, MRI, Evoked potentials and Urodynamics. The neurological status of the patients will be determined in terms of AIS.

During all follow up visits the investigator will evaluate and enquire for any adverse events in the study subjects. All adverse events will be recorded in the source CRF.

Electrophysiological studies such as motor evoked potentials, somatosensory evoked potentials, and electromyography to differentiate voluntary muscle contraction from reflex or involuntary spontaneous limb movement. The spinal MRI will be carried out to examine any changes in the spinal cord and surrounding tissues. Changes in activity patterns in the cortical sensorimotor networks will be measured using functional MRI during the proprioceptive stimulation with repetitive passive toe movement.

Functional neurological improvements will be estimated in change in the percentage of patients improving on the AIS scale.

To investigate the systemic effect of GM-CSF on the outcome of SCI, the number of white blood cells in the peripheral blood will be compared with the neurologic outcomes. The administration of GM-CSF has been used extensively to trigger peripheral leukocytosis and to induce bone marrow hematopoietic stem cell mobilization. The total

number of recruited white blood cells in the peripheral blood will be elevated after GM-CSF administration. The number of white blood cells in patients will be compared with improved neurologic function that in the patients without neurologic improvement.

Changes in the functional parameters using ASIA scale and MRI findings for the patients with treatment will be recorded. (Table 1) (Table 2)

Procedure related risk factors.

Risk of bleeding from bone marrow aspiration site

Post aspiration- transient pancytopenia, anemia, some times requiring transfusion.

6. Benefits

Potential benefits include increase in limb movements and overall bodily and general condition improvement, relief of rest pain and the ultimate benefit being prevention of productive life loss. Relief of incapacitating bedridden life with improved limb movements, apart from improving quality of life, help these patients return to productive life, especially in young manual worker would help him to return to their work and earn a living, preventing catastrophic financial and social hardship for the entire family.

Since the stem cells are derived from patients own bone marrow and ingredients used to enrich are also safe products used under GMP conditions, their usage will not produce any major adverse effects, mild fever is the anticipated side effect.

Other events may be Infection. Swabing with culture and sensitivity pattern to be done. Prophylaxis ceftriaxone 2 g at induction followed twice, 5 days.

Conservative management, head and elevation, observation, resuring, lumbar drain insertion and direct re-exploration and repair if needed.

Wound issues: like wound dehiscence, gaping might need resturing. Drug interactions in the form of allergic reactions will be dealt in accordance with critical care protocols. Anesthetic complications like airway obstruction, delayed recovery, respiratory failure, chest infections and drug reactions will be taken care of as per critical care protocols. Deep Vein Thrombosis if any will be attended.

Infection in the urinary tract which is caused by indwelling catheter will be treated as needed.

7. Concomitant Medications

The permitted medications will include antibiotics and analgesics in the post procedure period.

Table 1. *ASIA (American Spinal Injury Association) Impairment Scale.*

Classification	Description
A	Complete: no motor or sensory function is preserved below the level of injury, including the sacral segment S4-S5
B	Incomplete: Sensory, but not motor, function is preserved below the neurological level and some sensation in the sacral segment S4-S5
C	Incomplete: motor function is preserved below the neurological level, however, more than half of key muscles below the neurological level have a muscle grade less than 3 (i.e., not strong enough to move against gravity)
D	Incomplete: motor function is preserved below the neurological level, and at least half of key muscle below the neurological level have a muscle grade of 3 or more (i.e., joints can be moved against gravity)
E	Normal: Motor and sensory functions are normal.

Table 2. *Changes in MRI spine findings.*

MRI findings	Report
Change in spinal cord	
Diameter	
Decrease diameter	
No change	
Increase diameter	
Cord atrophy distal to the lesion	
Enhancement	
Cord edema	
Cystic degeneration	
Cyringomyelia	

8. Conclusion

Animal studies have demonstrated that transplanted MSCs modify inflammation in acute state and therefore reduces the effect of the inhibitory scar tissue in the subacute/chronic setting to provide good provision for axonal extension. Clinical data indicates the safety aspects of autologous bone marrow cell transplantation and/or GM-CSF administration can be used to treat patients with SCI. Future strategies to improve/enhance the axonal regeneration by Anti-Nogo-A, Chondroitinase-abc, Cyclic AMP to enhance neurons from the stem cells.

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