



Research Article

Clinical Safety and Efficacy of Autologous Mesenchymal Stem Cells in Spinal Cord Injury: A Clinical Trial Report

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Abstract

Background: The treatment of Spinal cord injuries (SCI) poses a major challenge to the medical fraternity. In this regard, autologous stem cells, such as bone marrow derived mesenchymal stem cells, (BMMSCs) could be an attractive option for treating SCI patients to some extent. However clinical studies are necessary for transferring preclinical findings from animal experiments to humans. We investigated the transplantation of autologous BMMSCs in patients with acute SCI with respect to safety, therapeutic time window, implantation strategy, number of doses and functional improvement. We report data from 20 patients (1:1) enrolled for the study with complete or partial transaction as shown by MRI. We report data of 20 patients who received transplants 6 weeks post injury. The follow up examination was done at 6 weeks, 12 weeks, and 24 weeks after implantation by the neurologistics using the standard neurological scoring including the Frankel score along with the improvement in the sensory and motor functions. **Objective:** This study was a prospective, randomized, open-label parallel group clinical study. Out of the 10 patients, two of the subjects enrolled in the treatment group received three doses at the interval of a month between the doses. The 10 patients enrolled in the treatment arm received the autologous stem cells along with the standard care, while the other 10 subjects received the standard care alone. MRI evaluation of the lesion was also planned at the follow up visits. The functional responses and the improvement in the quality of life of patients receiving multiple doses of the autologous cells were compared with the patients receiving single dose of cells. During the study period, patients were given standard care for management of acute SCI including surgery, decompression, immobilization etc. **Results:**

Patients enrolled in treatment arm (R-HSC-001 + Standard Care of management) with spinal cord injury have shown better improvement in motor function as assessed by Frankel score as

compared to control arm (Standard Care of management alone). 6 (66.67%) patients showed at least 1 grade improvement in Frankel score in treatment arm as compared to 2 patients (33.33%) in the control arm at the end of treatment. Patients who received three doses of investigational product have shown maximum improvement in Frankel score (improved from A to D). Muscle power improved in 4 patients (including two subjects who received three doses of IP) enrolled in treatment arm while in one patient enrolled in control arm. In treatment arm, patients who received three doses have shown better improvement in neurological function, as compared to patients who received only one dose of investigational product. 6 (66.67%) patients showed improvement in sensory perception in treatment arm as compared to 2 (33.33%) patients in control arm at the end of 24 weeks. **Conclusion**

1. At the end of the study, we could conclude that autologous BMMSCs was safe, well tolerated, easy to administer and efficacious to treat patients with spinal cord injury with the overall improvement in the quality of life.
2. Patients receiving multiple doses showed a maximum improvement in neurological functions with the overall improvement in the quality of life.
3. There was no safety concern in patients who received three doses of investigational product indicating the cells to be safe in multiple doses.
4. The frequency of adverse events was less in treatment arm as compared to control arm. In addition, there was no death reported in the test arm, hence stem cell therapy was found to be effective to recover the neurological functions.
5. Trials involving a larger population of patients, multiple routes and different cells doses are needed before further solid conclusion can be drawn.

Key words: Autologous bone marrow, mesenchymal stem cells, spinal cord injury, multiple doses

Introduction

The increasing incidence of traumatic spinal cord injury (SCI) affecting the younger population of the country is worrisome. As high as 44.5%, such injuries are caused by falling from a height, and a 34.78% as a result of motor vehicle accidents. To date, the available standard of care consists of stabilization of the spine, early administration of agents like methyl prednisolone early followed by surgical intervention as required. Post-stabilization, currently neurorehabilitation, seems to be the only hope for the affected. However, this is insufficient to help patients with SCI as the injury has a significant impact on the quality of life. The basic premise that neurons have is limited or no regeneration capability, after injury is being challenged by experts from various domains. This has led the way for a totally different approach to address such problems.

Regenerative medicine approaches using growth factors and various cell based therapies are particularly appealing, with early encouraging results from several groups [1,2,3]. Cellular transplantation after SCI is believed to bridge any gaps or cavities, replace dead cells, and create a favorable environment for axon regeneration.

Adult stem cells are undifferentiated cells found throughout the body that divide to replenish dying cells and regenerate damaged tissues. They are found in higher number during embryonic development and get lesser in adult life. They can be isolated from various adult tissues, grown and differentiated into specific cell types as per needs. Adult stem cells have the ability to divide and self-renew. Unlike embryonic stem cells, the use of adult stem cells in research and therapy is not controversial and does not have ethics related issues. Reports confirm that transplantation of MSCs into the preclinical animal models with SCI helped remyelination, helped axonal sparing resulting in functional improvement [4, 5].

Several other researchers have shown success following transplantation of stem cells at the site of the injury [6, 7]. During transplantation, the MSCs derived from bone marrow aspirate of the patient can be expanded and injected into the spinal cord of the patients as autologous cells.

Thus, much evidence points towards the ability of the MSCs to form glial and neuronal cells in response to genetic, chemical or physiological cues.

Therefore, stem cell therapy is likely to emerge as an attractive option for SCI treatment. Autologous bone marrow cells, olfactory sheathing cells, and Schwann Cells are other candidate cells under research to study regenerative mechanisms in the neurology segment.

Most studies for SCI have reported the use of mononuclear cell preparations from bone marrow, and in few studies, culture expanded MSCs have also been used.

It has been established through research that MSCs are immunosuppressive in nature; they reduce the acute inflammatory response following injury. These cells have also shown to have reduced the cavity formation and a decreased astrocyte and microglial/macrophage activity is also known to take place; however, whether it actively contributes to repair is yet not clear. MSCs secrete certain soluble factors by promoting the activation of the compensatory mechanism which leads to release of endogenous stem cells at the site of injury. This migration is hypothesized to be very useful for local reparative processes. Various studies have shown that MSCs stimulate glial cells and also promote axonal regeneration [8]. The neurotrophic factors, such as brain derived neurotrophic factor (BDNF), Nerve Growth factor (NGF), and vascular endothelial growth factor, (VEGF) secreted by MSCs promote the stimulation and activation of the injured spinal cord [9,10]. There are reports that show MSC conditioned media (MSC- CM) can also stimulate neurite out growth *in vitro* [9,11].

In this manuscript, we narrate the safety and efficacy of bone marrow derived from the autologous adult stem cells such as the mesenchymal stem cells (BMMSCs) in the treatment of SCI. The safety and efficacy of these cells was proven in the preclinical setting after an extensive *in vitro* study. This study thus provides the basis for the considering of MSCs favorably in the treatment of degenerative diseases such as spinal cord injury. Needless to say, larger studies in similar patients will be needed to bring a better understanding of dose, frequency etc. to be able to offer this as an alternative therapy.

Materials & Methods

Patient Selection

This was a prospective, randomized; open-label parallel group clinical study to evaluate safety and efficacy of bone marrow derived mesenchymal stem cells in patients with acute spinal cord injury. As per ICH-GCP & Schedule Y Guidelines, approvals from all study centers' Institutional Ethics Committees (IECs) were taken. Informed consent was obtained from every patient who participated in the study. Each patient was screened for HIV: [Human Immunodeficiency Virus]; HBV: [Hepatitis B Virus;] and HCV: [Hepatitis C Virus] antibodies. Any deviations, drop-outs and adverse events were documented and communicated to the IEC. A total of 20 patients of either sex were included in the study. The patients were randomized into two groups viz. Treatment arm (*R-HSC-001*) and Control arm. The test patients received Bone Marrow derived Mesenchymal Stem Cells (BMMSC) + the standard care, and the control patients received only the standard care. The standard care included medications such as methylprednisolone (Medrol), rest, analgesics and anti inflammatory drugs etc. Immobilization and surgery if required as may be the case. 20 subjects were planned to enroll (1:1 ratio to receive either R-HSC-001 + Standard Care or Standard Care) in the study to evaluate the safety and efficacy of R-HSC-001 in the treatment of spinal cord injury. A total of 11 patients were enrolled in

R-HSC-001 + Standard Care arm and 9 patients in Standard Care arm. One patient enrolled in R-HSC-001 + Standard Care arm died before IP administration.

R-HSC-001 is the code assigned to the BMMSCs during the clinical trials. The patients aged between 18 to 70 years, with acute thoracic (T2 to T12) or cervical spinal cord injuries (C1-T1) with complete or partial transaction/damage as evidenced by MRI, were eligible to participate in the study. All eligibly recruited patients were assigned a unique patient number and randomized in a ratio of 1:1 to be either under the test arm or the control arm. Patient groups are summarized in **Figure 1, flow chart**. Cases with gunshot injury, multiple spinal cord lesions, severe cognitive impairment, significant head trauma or any other injury - which could interfere with the assessment of spinal cord function or compromise the validity of the patient's data - were carefully

excluded. Also, patients with or patients on other experimental drugs 30 days prior to enrollment in this study, were excluded.

We excluded all patients who were hemodynamically unstable, those with evidence of meningeal inflammation, those with any immunological disorders, muscular dystrophies, or who are already participating in another trial actively, or had participated in a trial until one month prior to this.

The objectives of the study were:

Primary Objective:

- To evaluate the efficacy of BMMSCS in patients with acute spinal cord injury

Secondary Objective:

- To evaluate the safety of these cells in patients with acute spinal cord injury

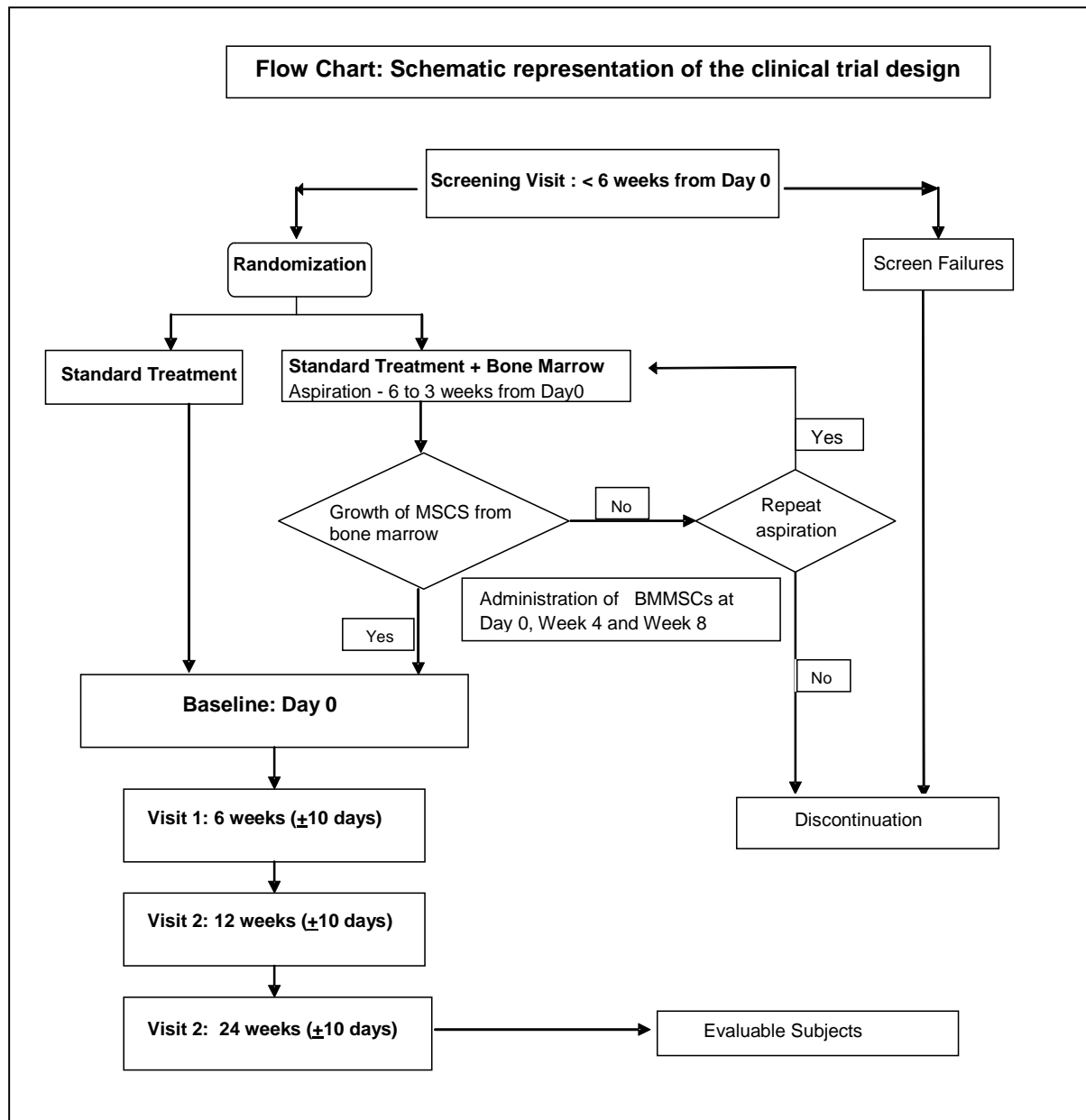


Figure 1: Flow Chart: Schematic representation of the clinical trial design

Separation of Bone Marrow Cells and Expansion of Mesenchymal Stem Cells

About 80-100 ml of bone marrow was aspirated from the iliac bone of the subject. It was transported in a cold chain to our GMP compliant cell therapy facility for isolation of

MSCs. The derivation and expansion of the Investigational Product (IP) took about 4-6 weeks. The bone marrow was processed as per the protocols published by Shetty et al; 2009 [12]. The mononuclear cells (MNCs) obtained by the published method were

plated for MSC expansion. The expanded MSCs at the end of the culture were characterized by the expression of mesenchymal markers by Flow cytometry. The viability of the cells was also checked using viaprobe. The IP was cryopreserved in liquid N₂ till the time of the transplant.

Operations

Pre-Surgical Procedure

All the patients were prepared appropriately for stem cell transplantation. Local anesthesia was given as per routine practice by the investigator team. The patients were positioned in recumbent position for the IP application.

IP Application Procedure

The cryopreserved cells were thawed as per the SOPs and aspirated into a sterile syringe for injection as per routine stem cell thawing procedures. All the harvested MSCs in passage 1 (P1) and passage 2 (P2) were administered sub-durally, slowly, below the site of the lesion and around it in an infiltrative manner. The number of cells injected into the subjects varied from 45 to 80 million cells. The patients were observed for two hours in the operation theatre. Most patients remained admitted due to their critical clinical condition. These were patients who required active nursing care on account of the spinal injury. They were discharged only after they were clinically stable. The follow up was performed at specific time points mentioned in the study protocol. With mutual discussion and based on newer observations in literature from various quarters and while the study protocol originally consisted of only one dose of IP for each patient, we elected to increase the frequency of the IP for which we sought a fresh approval from the drug controller, India. By the time we received the approval from the regulatory agencies for this change in the frequency on our protocol, we had just two more patients to be recruited into the study. The additional doses were given at week 4 and another one at week 8 after the first dose.

Post-Operative Care

The patients were discharged when they were clinically stable and followed up as per protocol for specific assessments at 6, 12 and 24 weeks post IP application.

Follow-up Schedule

The neurological status of the patients was determined using Frankel score.

Frankel score is an assessment tool used by the neurologists to measure clinical improvement in patients with neurological injuries. The grading system employed indicates the severity of the disease.

It has been in practice since the 1970's, which helped patients to be segregated into five categories, wherein A is the worst and E is normal; no function (A or Score 1), sensory only (B, Score 2), some sensory and motor preservation (C, Score 3), useful motor function (D, Score 4), and normal (E, Score 5). At each follow-up visit, the patients were clinically assessed using this score.

Muscular tone, sensory and motor function were assessed by traditional neurological assessments. Occurrence of any adverse event was noted and reported to the Data Safety Monitoring Board (DSMB) as per normal practice and the respective ethics committee, the mean duration of follow up was 6 months.

Assessment of Safety and Tolerability

1. Incidence and severity of adverse events assessed clinically and by laboratory tests
2. Local / systemic manifestations / reactogenicity assessed by evaluation of motor and sensory function.
3. Abnormal tissue or tumour formation was evaluated by MRI examination.

Statistical Analysis

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations were performed primarily using SAS (release 9.0 or higher) for Windows. The proportion of at least 1 grade improvement in Frankel score at the end of treatment was represented in

terms of counts and percentage. The *p* value was also derived by using a two tailed T test.

Results

Safety Results

No patients experienced any serious infections or complications that necessitated open surgery. There was a total of 7 patients with some minor adverse events in the treatment arm, but none of these could be related to IP. The most common adverse events in the treatment arm were fever followed by headache, back pain and gastric pain, while the control arm also reported fever and headache. The headache was mild in most cases and responded to analgesics. Fever could be controlled with antipyretics. Local injection site was unremarkable and there was no adverse event reported due to the IP administration per say. There was no itching, swelling or pain at the site of the

stem cell injections. All cases at follow up MRI's at the end of the study, in all cases, did not show any abnormal growth of tissues or tumour formation. Those who received additional doses of the stem cells also did not report any adverse events other than fever and mild headache. There was no other safety concern on account of additional doses of investigational product. MRI was tabulated in terms of counts and percentages by treatment group for Normal, Abnormal CS and Abnormal NCS (**Figure 2**). There was no abnormal tissue seen at the injected site either, till the end of the follow up. One patient did not experience any adverse event whatsoever during the entire study period. One death was reported in treatment arm, even before the administration of investigational product. Five patient deaths were reported in the control arm. This was perhaps due to progression of disease and the associated expected complications. All SAEs in the study were thus unrelated to the investigational stem cell product.

Variable	Visit	Grade	Treatment Arm (N=9)	Control Arm (N=6)
MRI	Screening		0 (0.00%)	0 (0.00%)
		Abnormal, NCS	1 (11.1%)	0 (0.00%)
		Abnormal, CS	8 (88.9%)	5 (83.3%)
	Pre IP Administration (Day -3 to -1) (Baseline)		0 (0.00%)	0 (0.00%)
		Abnormal, NCS	1 (11.1%)	0 (0.00%)
		Abnormal, CS	7 (77.8%)	0 (0.00%)
	Visit 1 Week 6 (+/- 10 Days)		0 (0.00%)	0 (0.00%)
		Abnormal, NCS	0 (0.00%)	1 (16.7%)
		Abnormal, CS	7 (77.8%)	2 (33.3%)
	Visit 2 Week 12 (+/- 10 Days)		0 (0.00%)	0 (0.00%)
		Abnormal, NCS	2 (22.2%)	1 (16.7%)
		Abnormal, CS	7 (77.8%)	3 (50.0%)
	Visit 3 Week 24 (+/-10 Days)		0 (0.00%)	0 (0.00%)
		Abnormal, NCS	5 (55.6%)	2 (33.3%)
		Abnormal, CS	2 (22.2%)	0 (0.00%)

Figure 2: Summary of MRI Examination-Evaluable population

Neuropathic Pain

Muscle power improved in 4 patients of whom two subjects had received three doses of IP. One patient enrolled in the control arm also showed improved muscle power. In the treatment arm, 6 patients showed improvement in sensory perception as compared to only two patients in the control arm at the end of 24 weeks of neurological assessment. Of these 6 patients, two have received multiple doses. Overall, within the

treatment arm, patients who received three doses showed better improvement in neurological function as compared to those who received only one dose of investigational product. Local and systemic manifestations/reactogenicity was evaluated by motor and sensory examination. The Motor examination parameters which included Gait movements formed the important part of the overall improvement of the patients. The parameters are tabulated in terms of counts and percentages (**Figure 3**).

Variable	Visit	Grade	Treatment Arm (N=9)	Control Arm (N=6)
Gait	Screening	Cannot Walk	9 (100.0%)	6 (100.0%)
		Walk With the Help	0 (0.00%)	0 (0.00%)
		Walk Without Help	0 (0.00%)	0 (0.00%)
	Pre IP Administration (Day -3 to -1)	Cannot Walk	9 (100.0%)	0 (0.00%)
		Walk With the Help	0 (0.00%)	0 (0.00%)
		Walk Without Help	0 (0.00%)	0 (0.00%)
	Treatment T1 Visit at Day 0 (Baseline)	Cannot Walk	9 (100.0%)	6 (100.0%)
		Walk With the Help	0 (0.00%)	0 (0.00%)
		Walk Without Help	0 (0.00%)	0 (0.00%)
	Treatment T2 Visit at Week 4	Cannot Walk	2 (22.2%)	0 (0.00%)
		Walk With the Help	0 (0.00%)	0 (0.00%)
		Walk Without Help	0 (0.00%)	0 (0.00%)
	Visit 1 Week 6 (+/- 10 Days)	Cannot Walk	6 (66.7%)	5 (83.3%)
		Walk With the Help	2 (22.2%)	0 (0.00%)
		Walk Without Help	0 (0.00%)	0 (0.00%)
	Treatment T3 Visit at Week 8	Cannot Walk	0 (0.00%)	0 (0.00%)
		Walk With the Help	2 (22.2%)	0 (0.00%)
		Walk Without Help	0 (0.00%)	0 (0.00%)
	Visit 2 Week 12 (+/- 10 Days)	Cannot Walk	4 (44.4%)	5 (83.3%)
		Walk With the Help	4 (44.4%)	1 (16.7%)
		Walk Without Help	1 (11.1%)	0 (0.00%)
Visit 3 Week 24 (+/-10 Days)	Cannot Walk	4 (44.4%)	4 (66.7%)	
	Walk With the Help	4 (44.4%)	1 (16.7%)	
	Walk Without Help	1 (11.1%)	0 (0.00%)	

Figure 3: Summary of the Gait

Neurological Improvement (Frankel Score)

In the test arm, there were 6 patients with Frankel score A, 3 patients with Frankel score B and 1 patient with Frankel score C. At 24 weeks of treatment, the neurological status of patients improved. At this time, there were 3 patients with Frankel score A, 2 patients with Frankel score B, 1 with Frankel score C and 4 patients with Frankel score D.

In the control arm, 4 patients with Frankel score A and 2 patients with Frankel score B were enrolled. At 24 weeks of treatment, neurological assessment of patients showed that only 2 patients remained at Frankel score A, 2 patients were at Frankel score B and 1 patient at Frankel score D.

The primary endpoint was improvement in Frankel score at the end of the treatment period. The improvement based on Frankel

score is shown in **Figure 4, Tables 1 & 2**. Patients in the treatment arm had shown

better improvement in motor function as compared to those in the control arm.

Table 1 –Individual Frankel Score Assessment

Treatment Arm					Control Arm				
Patient No.	Baseline	Scores	@24 wks	Scores	Patient No.	Baseline	Scores	@24 wks	Scores
13103	A	1	B	2	13101	A	1	-	0
13107*	A	1	D	4	13104	A	1	-	0
13108	A	1	A	1	13105	A	1	A	1
13201	B	2	C	3	13106	A	1	-	0
13202	B	2	A	1	13303	A	1	-	0
13301	A	1	B	2	13304	A	1	B	2
13302	B	2	D	4	13401	B	2	B	2
13402	A	1	A	1	13403	A	1	A	1
13404*	A	1	D	4	13405	B	2	D	4
13501	C	3	D	4					
Average		1.4		2.6	Average		1.2		1.1
<i>p value = 0.02</i>					<i>p value= 0.81</i>				
<i>Significant improvement in the Treatment arm as compared to the control arm (p value=0.028)</i>									
<i>*Received three doses of the investigational product</i>									

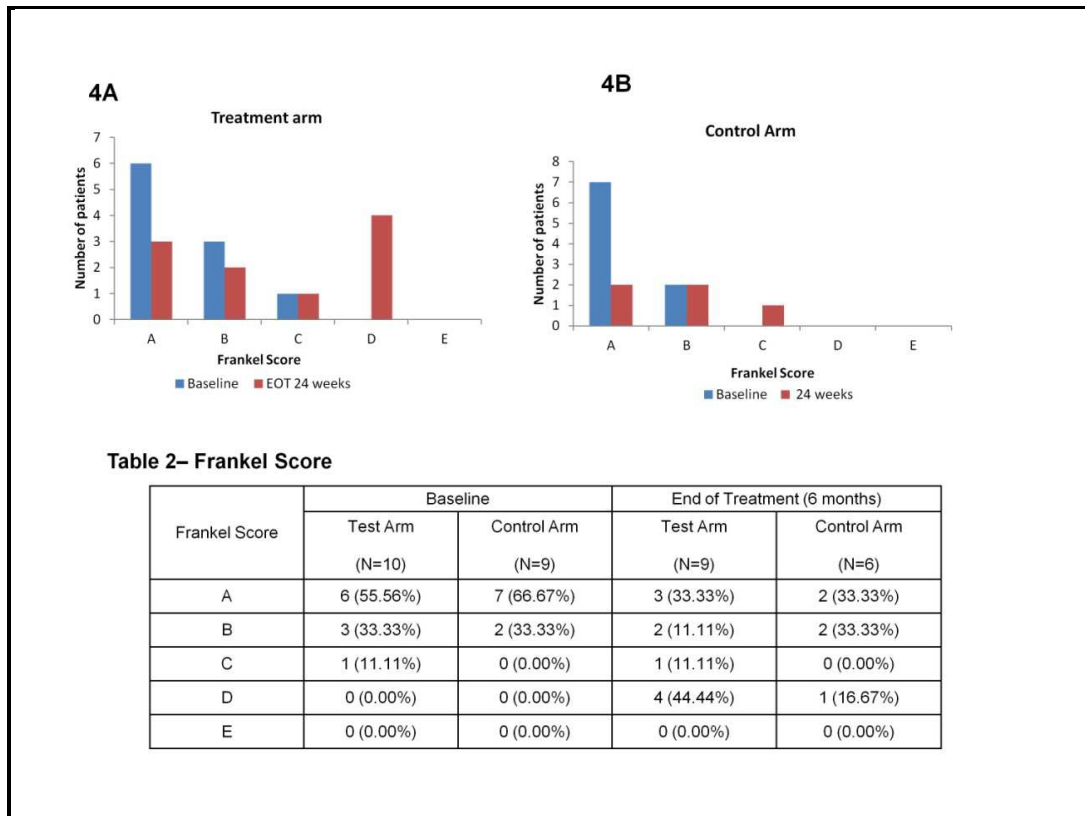


Figure 4: Frankel score

Efficacy Results

Overall patients in the treatment arm have shown improvement in motor function as compared to the control arm. In the treatment arm, six patients showed at least 1 grade improvement in Frankel score as compared to only 2 patients in the control arm at the end of treatment. Patients who received three doses have shown significant improvement in neurological function and Frankel score assessment as compared to those who received only one dose of investigational product.

Also, muscle power improved in 4 patients from the treatment arm and in 1 patient in the control arm group. At 24 weeks, 6 patients showed improvement in sensory perception in the treatment arm as compared to only 2 patients in control arm.

Improvement in neurological functions (Frankel score) is indicative of recovery of spinal cord injury and physiological function of spinal nerves.

Discussion

SCI represents a complex event with long term complications and associated morbidity. Effective therapeutic strategies normally consist of a series of interventions [13]. Clinical studies using surgical intervention for SCI have shown only marginal difference in neurological recovery [14]. Stem cell based therapies are thus being investigated by several researchers to check if the morbidity associated with this can be minimised and regeneration of damaged nerves and tissues can be improved. In that context, studies by Sykova et al (2006) [15] show that intravenous and intra arterial transplantation of mononuclear cells into SCI are safe and reasonably efficacious. Needless

to say that autologous BMMSCs in treatment of patients with SCI offer several advantages. Allogeneic sources could always have the risk of immunological reactions, as compared to autologous ones. But recently, positive developments have been observed even in the allogenic path [16]. In autologous mode, one has to do meticulous planning with regards to collection of bone marrow processing. One cannot forget the fact that quality and quantity of the marrow is sometimes affected by the age of the patient. To overcome these inconsistencies, several groups including ours, have investigated the use of alternative sources for deriving MSCs. MSCs derived from the other naive and non controversial allogenic sources like the umbilical cord have distinct advantages due to their good growth kinetics, differentiation potentials, banking ability, immunomodulatory functions and plasticity [17].

In our preclinical rat models with SCI, when treated with UCMSCs we found improved motor functions when cells were implanted within 4 weeks. It was found that the cells survived and differentiated into neurons and had a positive effect on functional and survival outcome (data not shown). The time of administration of cells after the injury, we feel, is quite crucial in determining efficacy. As there are limitations to understanding of dosage using observations from animal models; only a well designed clinical protocol could throw up some solid conclusions. There are limitations regarding dose and volume of cells injected through tail veins in small animals, and not all improvements are actually objective.

Thus, the definition of therapeutic window, the correct implantation strategy, the right method and route of administration, the number of cells needed and the possible side effects have evolved from clinical trials only. Ours was a phase I clinical study conducted to demonstrate safety, feasibility, of administration of BMMSCs and efficacy in such conditions. We also desired to get an indication on the possible dose, frequency of the stem cell administration and the quality

of life of these patients, post transplant. In this study, there were no infectious complications. Small adverse reactions occurred in a few cases, but were not related to the stem cell injections. Death was a severe adverse event noted in the study, but was attributed to the natural course of the injury and unconnected with the cell injections. Improved blood flow and improved oxygenation locally is a desired objective. Since BMMSCs possess angiogenic properties; we believe that the functional improvement seen in the transplanted patients was perhaps due to this attribute. The role of BMMSCs in angiogenesis, leading to improved regeneration, has been shown by several other researchers too [18,19].

For this clinical study, MSCs were isolated and expanded from a volume of about 40-100 ml bone marrow. All the expanded and characterized cells at passage 2 were then transplanted by infiltrating the half of the cells into the affected area and the immediate surrounding area. The remaining was injected into the intrathecal space a little above the injury site. There were no tumors or new growths observed up to 6 months which was the follow up period.

A clear improvement in the scores was observed in the test patients as compared to the controls. Again, interestingly, patients receiving 3 doses of BMMSCs had a higher level of improvement [3 grade improvement] as compared to those in the 'control group' patients. Sykova E et.al (2005) [20] reported data of 20 patients with SCI who received autologous BMMSCs. These authors were unsure if the observed beneficial effects were due to cell therapy or a natural improvement. In a similar study conducted by Park et.al (2005) [21], the improvement in motor & sensory function was observed but without randomized controls, which created some bias in crediting the MSCs for the gained response. Kishk et.al (2010) [22] injected monthly intrathecal autologous MSCs for 6 months. Patients, on receiving 6 doses of BMMSCs, showed '1 grade' improvement in ASIA score but minimal improvement in trunk support or sensation and partial

improvement in bladder & bowel movements. Overall, the degree of damage to the cord and the interval between treatment with stem cells and the injury is something that is much to be discussed. A local instillation of cells can definitely improve the cytokine availability at site and also the necessary milieu to improve neuronal regeneration. Instillation frequency of injection could, at best ensure consistency of this. The efficacy of the MSCs will depend also on the different routes of the cell application [23]. The cells used for the study are pure expanded autologous MSCs from passage 2 and not those that are differentiated into Oligodendrocytes or Neurons. It is believed that cells can be pushed to that lineage before they are instilled and injected, but there are controversies around this methodology. Also, fully differentiated cell will have lesser number of stem cells preventing extended action and local improvement. So, at the moment, it is prudent to give undifferentiated MSCs with a slight favoritism towards neuronal progression. That will be the target to be achieved. Patients with old spinal cord injuries were not part of the study. We deliberately excluded such cases, as dense fibrosis; extensive neuronal losses could influence the outcome of the study negatively. It remains to be seen if stem cells can cross this barrier of fibrosis and bring about functional changes.

Conclusions

The present study showed that undifferentiated MSCs were very safe. The cells were well tolerated, easy to administer and efficacious to treat patients with spinal cord injury. Injection of cells at the site of spinal cord injury does probably help in regeneration of axons and recovery of neurological functions to some extent. Higher the frequency better was the improvement. These observations are encouraging; this will pave the way to plan further studies in the future; future protocols should also include combinatorial therapy using other cells types such as hematopoietic stem cells and or

endothelial cells types in order to replace lost or damaged tissue. That will be a paradigm shift in the treatment options for patients with spinal injuries. As of now, research observations firmly indicate that cell therapies could definitely be considered, least for a few cases of SCI, who otherwise have no option left through currently available treatment modalities.

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