



Original Research Article

Role of Surgery, Omentoplasty and Autologous Bone Marrow Derived Mononuclear Cells Infusion on Clinical Outcomes After Spinal Cord Injury- A Randomized Controlled Trial

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ABSTRACT

Background: The hopelessness and helplessness experienced by spinal cord injury patients and treating doctors had triggered the innovations in the field of spinal cord injury management. Use of bone marrow mononuclear cells and stem/progenitor cells of desired lineage for the treatment of various diseases either alone or as add on to conventional treatment have shown promising results by several past and ongoing trials.

Study purpose: To evaluate neurological recovery in patients of acute thoracolumbar, complete spinal injuries managed by five different treatment modalities.

Patients and Methods: Total 110 patients (aged between 16-60 years) with unstable thoracolumbar spine injury (Thoracolumbar injury classification and severity score ≥ 4) between T9-L2 vertebra with complete paraplegia i.e. AISA (American Spinal Injury Association) grade 'A' with injury less than three week duration were randomly included for five different treatment modalities.

Results: Among all the treatment modalities the group second i.e. conventional + bone marrow mononuclear cells infusion had shown the most significant result followed by group four i.e. conventional + bone marrow mononuclear cells along with omentoplasty. The group with least significance was group 3 i.e. conventional + omentoplasty. The conventional alone and conservative group showed result varying between above ones.

Conclusions: The infusion of stem cells of bone marrow mononuclear cells along with conventional treatment among all the treatment modalities seems to augment neurological regeneration in SCI patients and indicate that BM derived stem cells may become valuable material for neurological problems as add on to conventional treatment in future.

Key words: Bone marrow mononuclear cells (BM MNCs), Bone marrow stem cells (BMSCs), Randomized controlled trial (RCT), Spinal cord injury (SCI), Thoracolumbar injury classification and severity score (TLICS).

INTRODUCTION

Spinal Cord Injury generally results in loss of function such as mobility or feeling. The more mobile thoracolumbar spine injuries are more common. According to WHO Spinal cord injury fact sheet N°384, November 2013, the world wide incidence of SCI estimated between 40 and 80 per million of population per year. ⁽¹⁾ In India approximately 20,000 new cases are reported without any sign of reduction. ⁽²⁾

High velocity injuries have severely exposed the limitations of the conventional managements of patients. Till date the aim of all the treatment modalities is to rehabilitate these patients early and in such a way that they can become independent and a useful part of our society. But the improvement in neurological status is still unpredictable and a lot of resources are being invested in this aspect. With this background, we have performed this study to evaluate the conservative management with four other possible types of surgical treatment modalities of SCI with complete paraplegia for selecting the best one among them.

The intrinsic repair is quite restricted after SCI because neurogenesis rarely occurs in the central nervous system. As a result stem cell transplantation has become a promising therapeutic option for SCI patients. This might be accomplished by transplanting stem cells into the damaged area and directing them to grow new, healthy tissue.

As according to several previous studies the use of stem/ progenitor cell bearing autologous BM and omentum 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 which are frequently caused in allogenic cell transplantation. ⁽³⁾ Second autologous cells/tissue infusion is considered safe by not being associated with carcinogenesis. ⁽⁴⁾

Goldsmith HS et al had described that omentoplasty provoke revascularization and through these vessels the underlying and adjacent brain receives increased blood flow, oxygen, omental neurotransmitters (dopamine, noradrenaline and acetylcholine) and neurotrophic factors (nerve growth factor and gangliosides). ⁽⁵⁾ Since then numerous claims are being made in favor of omentum transposition in chronic spinal cord injury ⁽⁶⁾ but there are only a few published reports with detailed outcomes. Duffill J et al stated that this procedure may have a definite role in the management of acute spinal cord injury as an adjunct to neural grafting and reconstruction using collagen bridges and neurotrophic factors. ⁽⁷⁾ But no any confirmatory study with detailed outcome has been found that could claim omentum as a good source for SCI management.

Extensive scientific data on bone marrow stem cells (BMSCs) have been accumulated from previous experiences in bone marrow cells transplantation for hematological disease. This has made cell therapy using bone marrow stem cells widely applicable and is being investigated clinically in various neurologic diseases also. Several animal and human studies have demonstrated the tissue regeneration approaches in the recovery of SCI. ⁽⁸⁻¹⁰⁾ Bone Marrow mononuclear cell transplantation for spinal cord Injury is a promising approach with several studies reporting varying efficacies in animal models and in humans, ⁽¹⁰⁻¹⁶⁾ but there are

only a few published reports with detailed outcomes.

Therefore it is necessary to find a safe and reliable way to obtain these cells from patients, develop a protocol for isolating, culturing and enriching these cells under 'Good Laboratory Practice' (GLP) guidelines, and check whether human cells have the same reparative effects in the laboratory and animal studies.

Research objectives:

Main objective:

- Role of surgery, omentoplasty and autologous bone marrow derived mononuclear cells infusion on neurological recovery in patients of acute thoracolumbar spinal cord injuries.

Secondary objectives:

- To analyze the rate of recovery of the patients at two different time intervals after the start of the therapy.
- To compare treatment outcomes between five different treatment modalities in this study.

MATERIALS AND METHODS

Selection and Description of Participants:

Our research work is ethically approved by the Institutional Stem Cell Ethics Committee of KGMU- UP, Lucknow- India. Eligible patients for this phase 2, open label trial were acute complete injuries between T9 and L2 spinal segments. The randomized controlled trial (RCT) design had randomized subjects in five groups as per treatment offered to them with informed consent. After randomization, intervention was undertaken between 3 and 21 days after the injury.

Total 126 patients {age 16 – 60 years} of thoracolumbar injury (T9 –L2 vertebra) with complete paraplegia {AIS –

A} within three weeks of injury were enrolled as per inclusion criteria.

Inclusion criteria

- 1) Age 16 – 60 years
- 2) Acute unstable injury (TLISS \geq 4)
- 3) T9 –L2 vertebral level
- 4) Injury < 3 weeks

Exclusion criteria

- 1) Associated with other injuries needing intervention
- 2) Subjects who are medically unfit for surgery
- 3) Subjects who do not give consent for participating in the study

The patients were randomized in five groups as per treatment to be given.

- *Group 1-* Patients managed by conventional method
- *Group 2-* Patients managed by conventional method along with autologous BM MNCs infusion
- *Group 3-* Patients managed by conventional method along with omental transposition
- *Group 4-* Patients managed by conventional method along with omental transposition and autologous BM MNCs infusion
- *Group 5-* Conservative (non surgical treatment) i.e. Control group

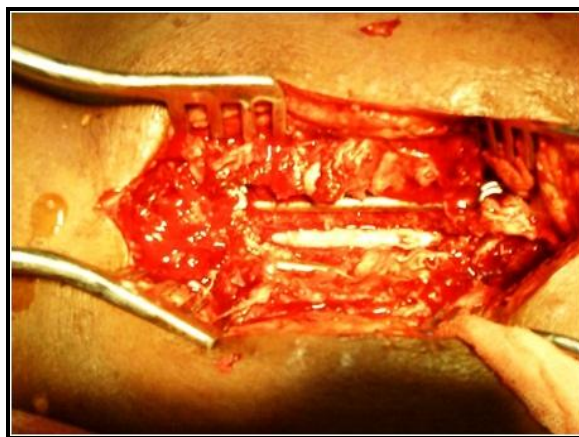


Figure 1: Posterior instrumentation with durotomy

Technical procedures and interventions:

The conventionally treated group 1 patients were managed by decompression of spinal cord with posterior instrumentation (Fig.1).

In the group 2 and 4 the patient after general anesthesia was laid prone to



Figure 2: Aspiration of bone marrow from posterior iliac crest

Aspirated bone marrow was allowed to sediment for some time. Processing was done by differential centrifugation at 1200 rpm for 10 minutes at 10⁰ C for RBCs and platelet separation as pellet using plasma expresser. The supernatant having plasma with most of nucleated cells was again centrifuged at 2500 rpm for 10 minutes at 10⁰ C. Using plasma expresser the precipitate (buffy coat) of mononuclear cells was collected as pellet after separating the supernatant having most of plasma and small nucleated cells (most of the granulocytes).

At the same time the patient had gone through conventional surgical intervention for decompression of injured spinal cord that includes stabilization by posterior instrumentation, durotomy and arachnoidectomy to visualize the damaged segment of spinal cord and nerve roots. During completion of surgical intervention an epidural catheter was passed in

aspirate 100-150 ml bone marrow from posterior iliac crest (Fig.2). The BM was collected in CPDA blood transfusion bag (Fig.3) followed by its processing using a self standardized differential protocol to isolate the BM MNCs within a totally aseptic condition.



Figure 3: Collection of bone marrow in CPDA blood bag

subarachnoid space and arachnoid and dura stitched back. Wound closure was done as per standard procedures with catheter in situ.

The processed autologous bone marrow derived mononuclear cell concentrate (i.e. collected pellet) was used to infuse through the catheter very slowly at the rate of 1ml/minute approximately (Fig.4). As the infusion completed the catheter pulled out carefully.



Figure 4: Infusion of BM MNCs at the site of lesion

For the group 3 and 4 along with other notified interventions the autologous omental transposition was done by

mobilization of omentum with intact pedicle to the site of lesion and its transposition over the spinal cord (Fig.5 & 6).

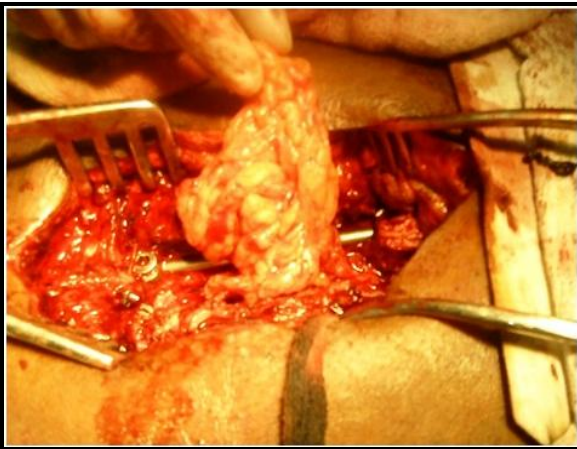


Figure 5: Mobilization of omentum with intact pedicle to the site of lesion



Figure 6: Transposition of omentum over the spinal cord at the site of lesion

Follow up: It was done at 6 weekly intervals for 1 year as per protocol and at each follow up patients were evaluated clinically and radiologically. The methodology (tools) to evaluate clinical endpoints for neurological recovery was AIS Scale. A data safety monitoring board ensured the ongoing safety of patients throughout the trial.

Statistical Techniques:

The data normalization was done by following formula-

$$\frac{\text{Grade score of particular grade} \times \text{Respective patients of that grade} \times 100}{\text{Total number of patients}} = \text{----} \%$$

Examples of Data equalization – as in group 1 at 6th month there are 23 patients with grade ‘A’ each having score ‘0’. On using the formula the percent mean recovery had found zero value. And patients in grade C (i.e. 5 patient with grade score for each = 2) had found the percent mean recovery equal to 33.33% as follows-

$$\frac{5 \times 2 \times 100}{30} = 33.33 \%$$

Using the same as above, we had charted the normalization table for descriptive analysis of the comparative recovery in each group. Using the normalized data obtained as percent mean recovery per patient for each group based on their grade score; we have done descriptive analysis of data to find out the percent mean recovery of each group using SPSS tool. We have also done the paired T-test and paired difference between the control group (group 5) and other four groups.

RESULTS

Total of 110 patients out of 126 enrolled patients were followed up to 1 year with the loss of 16 patients either due to death or due to unavailability at follow up. The mean age of the patients was similar among all 5 groups. Majority of the patients were male in all the groups. The Statistical analysis includes only those number of patients whose follow up had been completed. The number of patients in different ASIA grades and their corresponding percent total ASIA scores for

each group during follow up has been shown in table 1 and 2 respectively.

The recovery was higher in group 2 at 6 month and at 12th month. (Table 3)

Table 1- Number of Patients in different ASIA grades during follow-up:

Groups ↓	ASIA Grades →	Number of patients in different ASIA grades of each group during follow up														
		At admission					At 6 month					At 12 month				
		A	B	C	D	E	A	B	C	D	E	A	B	C	D	E
Group 1		30	0	0	0	0	23	1	5	0	1	23	1	4	1	1
Group 2		23	0	0	0	0	17	1	3	0	2	17	1	1	2	2
Group 3		17	0	0	0	0	15	1	1	0	0	15	1	1	0	0
Group 4		21	0	0	0	0	18	0	0	2	1	18	0	0	2	1
Group 5		19	0	0	0	0	17	1	1	0	0	17	1	0	1	0

Where ASIA A, B, C, D and E has grade score equal to 0, 1, 2, 3 and 4 respectively

Table 2- Calculated Normalization Table:

Groups ↓	ASIA Grades →	Total percent ASIA scores of all patients in each grade during follow up														
		At admission					At 6 month					At 12 month				
		A	B	C	D	E	A	B	C	D	E	A	B	C	D	E
Group 1		0	0	0	0	0	3.33	33.33	0	13.33	0	3.33	26.67	10	13.33	
Group 2		0	0	0	0	0	4.35	26.09	0	34.78	0	4.35	8.7	26.09	34.78	
Group 3		0	0	0	0	0	5.88	11.76	0	0	0	5.88	11.76	0	0	
Group 4		0	0	0	0	0	0	0	28.57	19.05	0	0	0	28.57	19.05	
Group 5		0	0	0	0	0	5.26	10.53	0	0	0	5.26	0	15.79	0	

Table 3- Percent mean recovery in each group:

Groups	Percent (%) mean recovery	
	At 6 th month	At 12 th month
Group 1	9.9980	10.6660
Group 2	13.0440	14.7840
Group 3	3.5280	3.5280
Group 4	9.5240	9.5240
Group 5	4.2100	6.6660

The paired difference between the control group and other four groups had shown the maximum recovery difference between control group and BM-MNCs infusion group. There was negative correlation between control group and only omentoplasty group. (Table 4)

Table 4- Paired T-test:

Pairs	Comparing Groups	Comparison of percent mean recovery between control (group 5) and other four surgical groups			
		At 6 th month	Difference of means	At 12 th month	Difference of means
Pair 1	Group 5	4.2100	5.7880	6.6660	4.0000
	Group 1	9.9980		10.6660	
Pair 2	Group 5	4.2100	8.8340	6.6660	8.1180
	Group 2	13.0440		14.7840	
Pair 3	Group 5	4.2100	- 0.6820	6.6660	- 3.1380
	Group 3	3.5280		3.5280	
Pair 4	Group 5	4.2100	5.31400	6.6660	2.8580
	Group 4	9.5240		9.5240	

Finally with the help of paired difference statistics we have found the beneficiary series of all treatment modalities i.e. as follows-

Group-2 (BM-MNCs + Conventional) > Group-1 (Conventional) > Group-4 (BM-MNCs + Omentoplasty + Conventional) >

Group-5 (Conservative) > Group-3 (Omentoplasty+ Conventional).

DISCUSSION

This study was designed to evaluate the role of newer interventions in the management of SCI.

Since clinical studies are necessary for transferring preclinical findings from animal experiments to humans. Therefore to achieve the goal of proving bone marrow as one of the best source for clinical treatment of SCI several animal experiments were done with success.

Ramer LM *et al* reported that the transplantation of bone marrow cells could promote functional improvements after SCI. (17) Sasaki *et al* (2001) studied potential of bone marrow cells to differentiate into myelin-forming cells and to repair the demyelinated rat spinal cord *in vivo* using cell transplantation techniques. (10)

The role of BMSCs in SCI has been clarified by Lee *et al* (2003) by the transplantation of mouse BMSCs into the mice subjected to SCI. By testing the expression of neuronal markers for the tissue samples located close to the transplanted site they have found that the sample had shown well expression of NeuN, MAP2 and doublecortin on fluorescent immunohistochemistry. (13)

Using the basis of therapy of SCI in Wister rat using BMSCs Zurita *et al* (2004) had shown progressive functional recovery proved by respective expressing of neuronal, astroglial and ependymal markers in the cases and controls. (14)

Neuhuber *et al* (2005) had done xenografting of human MSC into a subtotal cervical hemisection in adult female rats and found that cells integrated well into the injury site, with little migration away from the graft. The immuno cytochemical analysis demonstrated robust axonal growth, suggesting that MSC support axonal growth after spinal cord injury. (18)

Cao *et al* examined transdifferentiation of transplanted marrow stromal cells and reactive changes of glial cells in a completely transected rat spinal cord. (19) Shi *et al* showed MSCs enhanced angiogenesis in the rabbit host spinal cord

and improved the motor functional recovery after spinal cord ischaemia. (20)

Although above findings several other studies had shown that transplantation of bone marrow cells into the injured spinal cord found to improve neurologic functions in experimental animals. However, it was unclear whether bone marrow cells can similarly improve the neurologic functions of complete spinal cord injury in human patients or not.

Shen WJ, Shen YS (1999) did a retrospective review of the outcome of neurologically intact patients treated nonsurgically. They concluded that activity restriction and bracing may be important for pain control but probably does not change the long-term result. On, underwent at least two injections of their own hematopoietic stem cells. After cell transplantation, there was an increase of the muscle response amplitude to activation of motor nerve fibers of peripheral nerves. (21) This data was considered as indirect evidence that cellular therapy promotes spinal cord regeneration. Feron F *et al* and Huang H *et al* showed that significant functional recovery after cell transplantation was rarely achieved in the human clinical trials. (22,23)

To address this issue, Park *et al* evaluated the therapeutic effects of autologous bone marrow cell transplantation (BMT) in conjunction with the administration of granulocyte macrophage colony stimulating factor (GM-CSF) in six complete SCI patients. Sensory improvements were noted immediately after the operations. Significant motor improvements noted 3 to 7 months postoperatively. (15)

Few studies have been published that identify cell transplantation therapy as an ideal option for improving the neurologic function in patient at the chronic stage. (24,25) M. Baker (2009) presented his work on eight patients with spinal cord injury, received

surgeries that removing scar tissue, untethering the spinal cord and receiving infusions of cells collected from their own bone marrow. Patients were assessed for quality of life six months, one year and two years after the study, according to measures of bladder function, mobility and sensations. Almost all the patients reported some level of improvement on the measures assessed. (26)

Recently to assess the safety and therapeutic efficacy of autologous human bone marrow cell transplantation under a phase I/II open label and nonrandomized study was done on 35 complete spinal cord injury patients. In the control group, all patients (n=13) were treated only with conventional decompression and fusion surgery. At 4 months, the MRI analysis showed the enlargement of spinal cords and the small enhancement of the cell implantation sites. (27) These findings suggested the utility of BMSC transplantation in chronically established paraplegia. But it is yet to be confirmed that the observed beneficial effects are safe and worthy when unmanipulated autologous bone marrow cells are implanted in SCI patients.

Therefore to achieve the goal related to safety and efficacy of use of bone marrow products as synergistic aid to conventional procedure; we also transplanted autologous bone marrow derived mononuclear stem cell (CD34⁺) rich buffy coat in higher number of patients of spinal cord injury than the previous studies and observed good results with clinical safety and efficacy through open surgery transplantation. The groups using MNCs and omentum had shown no adverse effect during 1 year of follow-up.

All the procedures were done using GCP and GLP under the guidance of expert doctors and medical researchers of respective field. The conventional and conservative methods involved only the well

established protocols used world widely, while the methods that included the use of MNCs and omentum tissue were standardized by the corresponding team of research itself. The process of BM aspiration, isolation of its MNCs fraction and the infusion of MNCs at desired site has been well standardized following an ethically approved pilot study. Same was followed for omentoplasty. Use of autologous tissues and aseptic closed blood bag system during complete transplant procedure were two most significant and unique events of this study. This had been provided us the un-manipulated higher numbers of MNCs in the form of buffy coat as BM concentrate. The comparative result of follow-up of all the treatment modalities had shown that modality that only involve BM- MNCs had better result than others and this again proven the significance of BM derived products for the treatment of SCI. But to correlate the significance more strongly, it is required to increase the treatment sample size and follow-up time. Since various previous study had shown the doubtful significance of omentoplasty and our two groups that included omentum as aid on to conventional method either alone i.e. group 3rd or in conjunction with BM-MNCs i.e. group 4th were lower the significance of conventional method. Therefore our study proved that there is no significant role of omentoplasty in the better management of SCI.

CONCLUSION

- This can be inferred that the infusion of stem cell containing BM MNCs has significant role in facilitating neurological recovery in acute SCI
- Omentoplasty, have no influence in improving neurological recovery in our study, though not proven, and needs further study,

- Surgery, over conservative, has a definite role in providing stability and improving neurology in acute spinal cord injured
- These studies suggest that for the functional recovery of damaged spinal cord, human bone marrow stem cells can be transplanted into the spinal cord of patients. The bone marrow stem cell transplantation caused no new deficit in patients and appeared to be safe in short and longer term assessments.

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