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Outcome of Autologous Bone Marrow Aspirate Concentrate (BMAC) Transplantation in Patient with Spinal Cord Injury: Our experiences

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Abstract
Introduction: *Spinal cord injury (SCI) is a severe neurological disorder following trauma. Complete spinal cord injury ASIA Grade A with quadriplegia / paraplegia patients remains untreated and neglected in our country since long back. Now we planned effective strategy for the treatment of SCI by bone marrow derived mesenchymal stem cell transplantation has emerged as a viable therapeutic option with great potential for restoring neurological function following SCI.*
Summary: *From January 2016 to February 2017 a total of 10 SCI patient enrolled in our unit IV, Neurosurgery department, Dhaka medical college hospital, Dhaka, Bangladesh. All patients signed and given informed consent was taken prior to autologous bone marrow derived mesenchymal stem cell transplantation and bony decompression, fixation and fusion.*
Result: *Analysis of surgical outcome revealed significant improvement in motor, sensory and autonomic nerve function as assessed by the American spinal cord injury association impairement scale. 6 months after transplantation, a total of 10 patients, 9 patients demonstrated improvement. Among them 5 patients (50%) with Grade A SCI improved by one grade (i, e; Grade B), 3 patients (30%) with Grade A SCI improved by two grade (i, e; Grade C), 1 patient (10%) with Grade A SCI improved by three grade(i, e;Grade D). In all patient, post surgical extensive physiotherapy and regular follow up given.*
Keywords: *Spinal cord injury (SCI),Bone marrow aspirate concentrate(BMAC),American Spinal Injury Association(ASIA).*

Introduction

Spinal cord injury, is certainly a debilitating and devastating condition in terms of its effect on a person`s physical, mental, familial as well as social life [(1)]. Due to its profound impact on a person`s overall quality of life and increasingly

high incidence, injury to spinal cord due to any pathology is now considered as a morbid condition as well as a threat to both personal and national economy [2,3]. Spinal cord injury itself is a crippling condition, at the same time may lead to a variety of complications which can affect the life of the patient as it increases the treatment cost significantly and accelerate the disease process which link to early mortality [1,3,4].

Every year, around the world, between 250 000 and 500 000 people suffer a spinal cord injury (SCI).The majority of spinal cord injuries are due to preventable causes such as road traffic accident, falls, violence, sports injury etc. There is no reliable estimate of global prevalence, but estimated annual global incidence is 40 to 80 cases per million populations. Up to 90% of these cases are due to traumatic causes, though the proportion of non-traumatic spinal cord injury appears to be growing. Males are most at risk in young adulthood (20-29 years) and older age (70+). Females are most at risk in adolescence (15-19) and older age (60+). Studies report male-to-female ratio of at least 2:1 among adults, sometimes much higher. Mortality risk is highest in the first year after injury and remains high compared to the general population. People with spinal cord injury are 2 to 5 times more likely to die prematurely than people without SCI. Mortality risk increases with injury level and severity and are strongly influenced by availability of timely, quality medical care. Transfer method to hospital after injury and time to hospital admission are important factors [5].

The repercussions of spinal cord injury (SCI), regardless of origin, are often severe and include loss of bowel and bladder control, impairments in sensory and motor function and intractable pain. Despite current treatment strategies, including surgical decompression and fixation, the injection of neurotropic factors, anti-inflammatory medications and physical rehabilitation, satisfactory therapeutic effects remain elusive [6].

Stem cell transplantation at the site of injury has emerged as a possible alternative therapy for severe spinal cord injury [7] Human bone marrow-derived mesenchymal stem cells (HBMSCs), identified alongside hematopoietic stem cells and possessing tremendous capacity for self-renewal and differentiation, are a type of adult stem cell that have demonstrated positive effects in the treatment of SCI [8,9].

In the current study, we report on surgical outcome of autologous bone marrow aspirate concentrate (BMAC) transplantation in 10 patients of SCI treated at Dhaka Medical College Hospital, Dhaka, Bangladesh. In addition to BMAC transplantation in the cord, decompression and fixation of respective fragmented unstable vertebral column was done. A total of 10 SCI patients were enrolled in our study at Dhaka Medical College Hospital, Bangladesh from January 2016 to February 2017.

Materials and Methods

There were 8 male patients (80%) and 2 female patients (20%) aged ranged from 11-70 years, with an average age of 31.5 years. According to the American Spinal Injury Association's classification of SCI (ASIA impairment scale) all the 10 cases were of grade A. Among all SCI patients, there were 4 cases involving the cervical region, 6 cases involving the thoracic region. When divided into the etiology of SCI, there were 5 cases caused by RTA and 5 cases are fall from height. Written informed consent were obtained from all participants before intervention.

Fig-1 Pre operative X ray of SCI

Post operative X ray after fixation

Transplantation methods

Preparation of autologous bone marrow aspirate concentrates (BMAC)

Under aseptic conditions, Bone Marrow Aspirate Concentrate (BMAC) was isolated from BM aspirates from respective SCI patients. BM aspirates was obtained according to standard procedures: 60 ml of BM aspirate was taken from the posterior superior iliac crest and placed immediately into a sterile bag containing 4 ml of ACD solution. All subsequent processing was done under complete aseptic conditions. Then the aspirate was filtered from the bag and placed in a container and centrifuged for 14 min at 4000 rpm at room temperature. The supernatant plasma, Buffy coat were discarded, and the nucleated cells which were precipitated are collected in a special syringe and transplanted at the site of injury immediately. Before transplantation in the cord, decompression and bony fusion of the vertebral column was done.

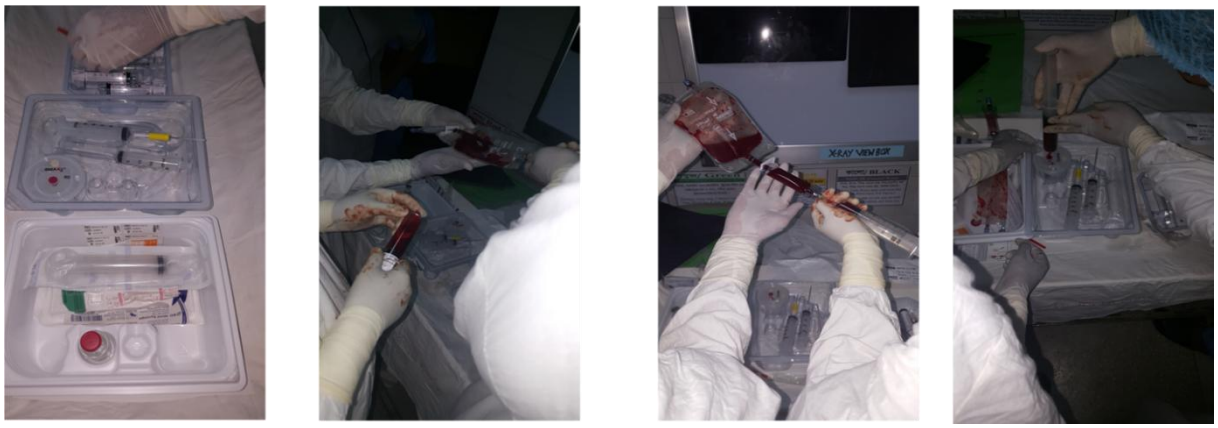

Fig-2 Preparations of bone marrow aspirate concentrate (BMAC)

Fig-3 Stem cell in the bucket

Stem cell aspirated in the syringe

Cell transplantation

After adequate decompression by laminectomy, partial corpectomy and discectomy followed by stabilization with transpedicular rod and screw was done, Durotomy at the site of injured spinal cord was done. Then the CSF pathway was made established, contused cord element and fibrin debris were made clear and prepare the site for transplantation. Then the centrifuged BMAC was transplanted in the local injured site and in the subarachnoid place. Then the dura was closed. A total of 6 ml BMACs were injected into each SCI patient.

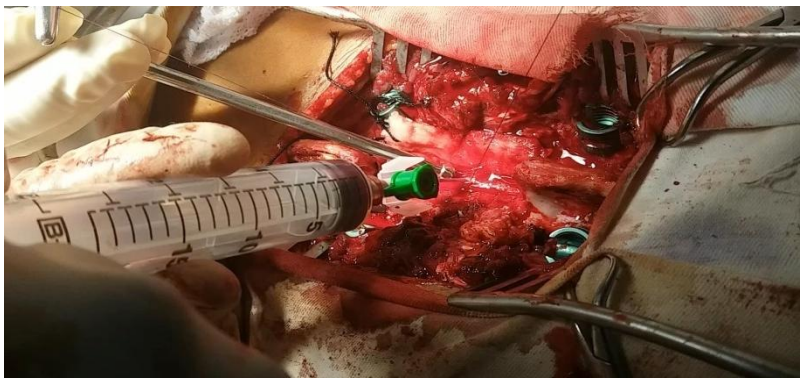

Fig-4 Stem cell placement at the site of injured cord

Neurological grading

Neurological grading was performed using the ASIA impairment scale as follows: Grade A, complete: no motor or sensory function is preserved in the sacral segments S4-S5; grade B, incomplete: sensory but no motor function is preserved below the neurological level and includes the sacral segments S4-S5; grade C, incomplete: motor function is preserved below the neurological level and more than half of key muscles below the neurological level have a muscle grade <3; grade D, incomplete: motor function is preserved below the neurological level and at least half of the key muscles below the neurological level have a muscle grade of ≥3; and grade E, normal: motor and sensory function is normal.

All the patients were assessed for ASIA grading on the day prior to transplantation, as well as at regular intervals following treatment

.

Table 01: Basic information of patients when admitted to hospital

Number	Gender	Age (years)	Injury site	Cause of injury	ASIA grade
1	F	11	T11-T12	RTA	A
2	M	35	T11- T12	RTA	A
3	M	50	C5-C7	FALL	A
4	M	45	C3-C4	FALL	A
5	M	17	T10-T11	FALL	A
6	M	30	T11-T12	RTA	A
7	M	70	T3-T4	FALL	A
8	M	18	C5-C6	FALL	A
9	F	11	C5-C6	RTA	A
10	M	28	T7-T8	RTA	A

ASIA: American Spinal Injury Association.

Table 02: ASIA grading before and after cell transplantation

ASIA rating before transplantation	Initial cases (n)	ASIA grading Improvement 6 months after transplantation					Number of cases presenting improvement
		A	B	C	D	E	
A	10	1	5	3	1	0	9(90%)
Total	10	1(10%)	5(50%)	3(30%)	1(10%)	0(0%)	9(90%)

ASIA: American Spinal Injury Association

Urinary and bowel function

Acute retention is a common issue for SCI patients. Assessments of bowel and bladder function are integral components of the Barthel activities of daily living (ADL) index. In order to better qualify the Barthel ADL index measures, however, these measures were subdivided. Bladder dysfunction was divided into no automatic micturition, incontinence, difficulty in urination, poor urine control and dribbling urine. Bowel dysfunction was divided into constipation, fecal incontinence and dry stools.

Results

Neurological grading by ASIA impairment scale

The post interventional result was evaluated after 6 months in the form of motor, sensory and autonomic.

Our analysis of the 10 SCI study patients receiving autologous BMAC transplantation was notable for all patients exhibiting improvement in sensory and motor function. Of the 10 SCI study patients, 9 individuals (90%) improved by one or two or three grades as measured by the ASIA impairment scale where 5 (50%) of those 10 patients improving by one grade, 3 (30%) of the 10 patients improving by two grades and 1(10%) of those 10 patients improving by three grades. One patient did not shown any improvement (Table 02).

The prognosis of SCI patients appears to be dependent on the stage of SCI, the cause(s) of SCI and patient age. Considering the multiple disparate characteristics of our study patients, we compared the therapeutic effects of autologous HMAC transplantation on SCI patients according to the variables in Table 03.

Assessment of urinary and bowel function

Of our 10 individuals (100% of the total SCI study subjects) suffering from urinary dysfunction in the form of acute retension. Patient recovery information is shown in Table 04. 10 patients (100%) present to us with acute urinary retention requiring catheterization. Of the ten SCI individuals suffering from urinary dysfunction, 80% (8/10) experienced post-stem cell transplantation improvement in urinary function to varying degrees.

Of the 10 individuals (100% of the total SCI study subjects) suffering from bowel dysfunction, in the form of dry stool. Patient recovery information is listed in Table 05. Of the 10 individuals 8 cases (80.00%) experienced post-stem cell transplantation improvement in bowel function to varying degrees.

Table 03: Different variables impacting the efficacy of stem cell transplantation

Factors	Initial cases (n)	Cases improved 6 months after cell transplantation (n)	Improvement rate (%)
Cause of injury			
Trauma			
RTA	5	5	100.00
FALL	5	4	80.00
Non-trauma	0	0	0.00
Site of injury			
Cervical vertebrae	4	4	100.00
Thoracic vertebrae	6	5	83.33
Age (years)			
<18	3	3	100.00
18-60	6	5	83.33
>60	1	1	100.00
Gender			
Male	8	7	87.50
Female	2	2	100.00

Table 04: Recovery of urinary function in spinal cord injury (SCI) patients

Types	Initial cases (n)	Cases improved 6 months after cell transplantation (n)
Acute Urinary retention	10	2

Table 05: Recovery of bowel function in spinal cord injury (SCI) patients

Types	Initial cases (n)	Cases improved 6 months after cell transplantation (n)
Hard stool	10	8

Discussion

A series of animal experiments [10,11] and clinical trials [12,13] have previously demonstrated that stem cells have beneficial effects for SCI. Our study demonstrates that motor and sensory dysfunction, urinary and bowel functional disorders may improve significantly following stem cell transplantation.

A study using Human Bone Marrow Mesenchymal Stem Cell (HBMSC) transplantation for the treatment of SCI (12) demonstrated that 29.5% of patients in the acute stage (<2 weeks) experienced an improvement in ASIA impairment rating from grade A to either B or C. Additionally, 33.3% of patients in the subacute stage (2-8 weeks) experienced an improvement in ASIA impairment rating from grade A to either B or C; while no improvement in ASIA impairment scale occurred in the chronic (>8 weeks) group.

In our current study, 90% of SCI patients experienced an improvement in ASIA grading, with the majority of these patients receiving stem cell transplantation and adequate decompression immediately after SCI with the exception of one patient who was in the chronic (after 1 year) SCI stage by laminectomy and removing soft tissue . Stem Cell therapy appears to have been more beneficial for the patients in the current study than for those in the study by Yoon et al,. In theory, the higher the grade, the greater the improvement; however, our data suggests an inconsistency with this theory as because our all samples were complete spinal cord injury with lowest grading . In addition, while our study followed-up patients for more than six month, Yoon et al continued for 10.4 months. In our study among 10 SCI patient 5 patients improved one grade, 3 patients improved two grade and 1 patient improved 3 grade and 1 grade does not improved yet at all but patient may improve in subsequent follow up.

Normal urinary and bowel function make a significant contribution to quality of life. Of the 10 SCI patients (100% of total) reporting urinary dysfunction, 20% experienced improved micturition following stem cell transplantation. In the study by Kishk et al [14] where no patients experienced complete recovery in urinary function, but in our study one patients experienced a return to normal function and other with dribbling urine prior to stem cell therapy. All 10 patients having bowel dysfunction in the form of hard stool, 80% experienced an improvement in function following stem cell therapy; this result is commensurate with the results from the study by Kishk et al. In addition to aiding the functional integrity of autonomic nerves for normal urinary and bowel function, the return of intestinal secretions following stem cell transplantation may have ameliorated a significant factor in the bowel dysfunction in certain patients.

Conclusion

Although limitations exist, BMAC transplantation has demonstrated its effectiveness for the

treatment of SCI. The majority of our patients clearly benefited from transplantation with notable improvements in sensory, motor and autonomic function. The mechanisms by which stem cells benefit SCI patients, however, are not fully clear. Currently, the mechanisms by which stem cells are believed to repair damaged tissue include the secretion of neurotrophic factors, the ability to re-wrap injured nerve fibers suffering demyelization and the formation of neural circuitry by transplanted cells that are able to differentiate into neurons [16-18]. However, despite steadily accruing evidence in support of the therapeutic benefits of stem cell transplantation, universal consensus regarding the mechanisms of action does not yet exist. Additional studies of autologous BMAC transplantation for the treatment of SCI remain a critical pursuit.

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