Int J Clin Exp Med 2020;13(3):1979-1986
www.ijcem.com /ISSN:1940-5901/IJCEM0103638

Original Article

Therapeutic effect of mesenchymal stem cell in spinal cord injury

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Received October 17, 2019; Accepted November 20, 2019; Epub March 15, 2020; Published March 30, 2020

Abstract: Objective: To explore the effect of bone marrow mesenchymal stem cells (BMSCs) transplantation in the treatment of spinal cord injury (SCI). Method: 68 SCI patients admitted to our hospital were randomly divided into group A and group B, with 34 cases in each group. Group A received autologous BMSCs transplantation therapy and group B received standard occupational therapy. The American Spinal Injury Association (ASIA) score was used to assess the recovery of neurological function before and after treatment. The Self-rating Anxiety Scale (SAS) and the Self-rating Depression Scale (SDS) were used to evaluate the psychological state of the two groups before and after treatment. The Health Status Survey (SF-36) was used to evaluate the life quality of the two groups after 6 months of discharge. The clinical efficacy and adverse reactions of the two groups were observed. Result: The effective rate of group A was significantly higher than that of group B ($P<0.05$). The motor, pain and tactile scores of the ASIA scores in group A were significantly higher than those in group B ($P<0.05$). The SAS and SDS scores of group A were significantly lower than those of group B ($P<0.05$). The scores of overall health, physiological function, social function, physical pain, physiological function, vitality, mental health and emotional function in SF-36 of group A were significantly higher than those of group B ($P<0.001$). After BMSCs transplantation, 1 patient developed low back pain, 2 patients developed fever, and 1 patient developed headache but did not receive special treatment. Conclusion: BMSCs transplantation has a good therapeutic effect on SCI compared with the standard occupational therapy. It can promote the recovery of neurological function in patients, and alleviate the patient's bad mood and improve the quality of life, with fewer adverse reactions, which may be an ideal treatment for SCI.

Keywords: Bone marrow mesenchymal stem cells, spinal cord injury, clinical efficacy, life quality

Introduction

Spinal cord injury (SCI) refers to damage to the spinal cord caused by external shocks. The injury may occur in a certain segment or across several segments. Pathological reflexes, abnormal muscle tone, and central nervous system trauma such as sensory, motor, and muscular dysfunction can occur at different stages of injury. In severe cases, paralysis may occur [1, 2]. With the occurrence of work-related injuries and frequent traffic accidents, the number of SCI cases has increased year by year. This not only endangers the health of patients, but also brings huge burden to families and society [3]. At present, the methods for treating SCI include surgical treatment, drug treatment and rehabilitation treatment. These treatments have alleviated the progress of SCI to a certain extent, but it is not possible to obtain a better clinical efficacy [4]. Although these treatments have a certain improvement effect on the neurological function and daily activities of SCI, the neurological function repair in patients with SCI is limited, and the incomplete recovery of neurological function may cause paralysis in patients. It is complicated by complications such as urinary tract infections and pressure sores [5, 6].

With the continuous research on the clinical treatment of SCI, stem cell transplantation provides a new therapeutic approach for the treatment of SCI. It is expected to be an effective treatment for nerve injury reconstruction or regeneration in patients with SCI [7]. Stem cells are a group of cells that are highly proliferating and self-renewing. These cells can divide themselves to maintain their size and can differentiate into different tissue cells. In the clinical,

they have the characteristics of large number of cells, complete types, small volume, and strong cell activity [8]. Bone marrow mesenchymal stem cells (BMSCs) are clinically available, easy to isolate and culture, and are obtained by themselves, so there is no immune rejection [9]. BMSCs can differentiate into a variety of cells including nerve cells under appropriate stimulation signals, and have a good application potential in the treatment of SCI [10].

Previous stem cell transplantation for SCI was mostly concentrated in *in vitro* experiments [11-13]. As studied by Kim et al [12], BMSCs are considered to be promising candidates for SCI, and treadmill exercise can enhance the motor function of SCI rats after BMSCs transplantation. In the study of Lin et al [13], BMSCs can improve the functional recovery of SCI by promoting axonal regeneration. But there are very few studies on the specific applications in clinical practice. The exact efficacy and safety of BMSCs transplantation for SCI in clinical practice remain unclear. In this study, BMSCs were used to treat patients with SCI, and the specific clinical efficacy and safety of BMSCs in the treatment of SCI were observed, which was intended to provide a reference for the clinical treatment of SCI.

Materials and methods

Baseline data

68 SCI patients admitted to our hospital were selected as subjects and randomly divided into group A and group B, with 34 cases in each group. Group A received autologous BMSCs transplantation therapy and group B received standard rehabilitation therapy. Thoracic spinal cord injury was assessed according to the American Spinal Injury Association (ASIA) damage classification [14]. The study has been approved by the ethics committee of our hospital. The subjects and family members were informed and signed the informed consent form.

Inclusion and exclusion criteria

Inclusion criteria: patients who met ASIA criteria for SCI [15] after CT/MRI imaging examination; no compressive lesions at SCI; hospitalized for 1 month or more; with an age less than 60 years; with stem cell adaptation disease.

Exclusion criteria: patients with adhesions at the injury site requiring surgical intervention; patients with symptoms of infection at the waist and ankle; patients with a high degree of allergies or a history of severe allergies; patients with progressive neurological decline due to unexplained reasons; patients who cannot be in prone position or the duration of prone position <20 min; patients with mental illness or a family history of mental illness; patients with severe hepatorenal dysfunction, spinal tuberculosis, spinal or dural vascular malformation, connective tissue disease, endocrine metabolic disease, nervous system disease, hematopoietic dysfunction, and immune disease; patients with severe pressure ulcers.

Treatment method

Rehabilitation treatment was given to both groups, including physical and occupational therapy. Joint rehabilitation training: passive and active training patterns were taken based on the patient's physical condition. It mainly focused on shoulder, wrist, elbow, knee and other joint trainings. In the early stage, passive training was used. After that, active training was started, and the intensity and frequency of training were improved. The stability of the spine was maintained during the training process. The training was 30 min each time, twice a day. Life rehabilitation training: patients were trained in daily activities such as dressing, eating, urinating and washing. Respiratory training: patients were given retrial breathing and resistance breathing training for 5 min each time, 4 times a day. Exercise rehabilitation training: patients were trained in decubitus position, elevation or sitting up, and combined with roll training. In the later stage, the patient needed to perform sit-up and standing balance training, and finally carried out walking training. Bladder and anal sphincter training: the patient was trained to contract the bladder. The patient was instructed to perform anal training to restore normal urination and defecation function. The course of rehabilitation treatment was 1 month.

BMSCs were extracted for treatment of group A, and standard rehabilitation treatment was given before and after surgery.

Bone marrow collection method: epidural anesthesia was performed on the patient in a sterile

operation room, and bone marrow puncture was performed after the onset of action.

The patient was in supine position, the buttocks were raised, and the puncture position was fully exposed. After routine disinfection, the sacral or anterior superior iliac spine was used as the puncture point, and the bone marrow was extracted by syringe containing bone marrow anticoagulant, and 15 mL was taken each time. 3-5 punctures were selected on each side, and each point was taken 3 times, and the bone marrow volume was 200 mL. The separation was completed within 4 hours after the bone marrow was taken. Bone marrow was isolated and extracted using a bone marrow stem cell extraction kit (Ningxia Zhonghang Biological Co., Ltd., China). Extraction method: bone marrow was mixed with liquid A and liquid B. After standing for 20 min, the mature blood cells were discarded, and the supernatant was centrifuged. The centrifugal force was 1200 g, the radius was 15 cm, the temperature was 25°C, and the mixture was centrifuged for 5 min. After the bottom cells were collected, the solution A was added and centrifuged for 5 min. The supernatant was discarded, and then placed in a solution C test tube, centrifuged for 5 min. The intermediate cell layer was aspirated, washed with solution A for 3 times, and centrifuged for 5 min. The stem cells were collected. A 25 μL volume of a cell suspension (amount of one transplant site) was prepared using physiological saline at a concentration of 8×10^5/μL. Stem cell transplantation was performed under CT guidance. The upper and lower spinal cord nearest to the injury was used as the target for the proposed transplantation to define the proposed puncture intervertebral space. After local anesthesia with lidocaine, the puncture needle was slowly inserted into the site to be punctured. After the CT scan confirmed that the puncture needle had entered the spinal cord, the stem cell suspension was injected, and the puncture needle was slowly extracted after 5 min of standing.

The patients were placed in a prone position for at least 5 hours. Each patient underwent 2 bone marrow stem cell transplantations. The interval between the two operations was 10 days, and the puncture site was the same site.

Comparison of thermoplastic effects

The therapeutic effects of the two groups after one month of treatment were observed [16]. Markedly effective means that the spinal cord function is recovered to level 2 or above, the function of the bowel and bladder is basically normal, and the motor and sensation are significantly improved compared with that before treatment.

Effective means that the spinal cord function is recovered to level 1 or above, the function of the bowel and bladder is basically normal, and the motor and sensation are improved compared with that before treatment.

Ineffective means that the function of the bowel movement, movement and sensation are unchanged compared with that before treatment. Total efficiency = (number of markedly effective cases + number of effective cases)/total number of cases × 100%. The ASIA score [17] was used to assess the recovery of neurological function before and 1 month after treatment, including motor function, sense of pain and tactile sense.

Motor function: A total of 10 muscle groups in the extremities, and the function of the upper and lower extremity muscle groups were assessed. According to the muscle strength grading standard [18], the upper and lower limb muscle group functions have 50 points each, with a total score of 100 points. Sense of pain and tactile sense include 28 points in a whole body. If missing, it is 0 point. If there is an obstacle, it is 1 point. If normal, it is 2 points. The total score of sense of pain and tactile sense on the left and right sides is 56 points, with a total score of 112 points. The higher the score, the better the recovery of neural function.

Self-rating Anxiety Scale (SAS) [19] was used to assess the anxiety status of patients before and 1 month after treatment, with a total score of 100 points. A score of 50-70 indicates mild anxiety, a score of 71-90 indicates moderate anxiety, and a score of >90 indicates severe anxiety. The higher the score, the more severe the anxiety. The Self-rating Depression Scale (SDS) [20] was used to assess the patient's depression status, with a total score of 100 points. A score of 50-70 indicates mild depression, a score of 71-90 indicates moderate depression, and a score of >90 indicates severe depression. The higher the score, the more severe the depression.

Table 1. Baseline data for group A and group B [n (%)]/(x±sd)

Category	Group A (n=34)	Group B (n=34)	t/χ^2 value	*P* value
Gender			0.086	0.770
Male	27 (79.41)	26 (76.47)		
Female	7 (20.59)	8 (23.53)		
Age	35.29±8.04	34.67±7.59	0.327	0.745
BMI (kg/m^2)	22.47±2.68	22.94±2.19	0.792	0.431
Cause of damage			1.081	0.582
Car accident	12 (35.29)	14 (41.18)		
Bruise	9 (26.47)	11 (32.35)		
Fall from a height	13 (38.24)	9 (26.47)		
Injury to hospital stay (months)	20.67±5.31	21.07±4.28	0.342	0.734
Damage site			0.258	0.612
Cervical pulp	23 (67.65)	21 (61.76)		
Thoracic marrow	11 (32.35)	13 (38.24)		
ASIA rating			0.345	0.842
Class A	22 (64.71)	20 (58.82)		
Class B	7 (20.59)	9 (26.47)		
Class C	5 (14.71)	5 (14.71)		
History of smoking			0.530	0.467
Yes	19 (55.88)	16 (47.06)		
No	15 (44.12)	18 (52.94)		
Drinking history			0.620	0.431
Yes	22 (64.71)	25 (73.53)		
No	12 (35.29)	9 (26.47)		
Glu (mmol/L)	5.81±0.62	5.94±0.77	0.767	0.446
ALT (U/L)	23.68±10.25	25.73±11.04	0.794	0.430
AST (U/L)	19.26±8.91	18.31±9.58	0.423	0.673

The Health Status Survey (SF-36) [21] was used to assess the patient's life quality after 6 months of discharge, including overall health, physical function, social function, physical pain, physical function, vitality, mental health, and emotional function, 8 items in total. The original score is converted to a percentage point. The higher the score, the better the life quality.

Adverse reactions such as backache, headache and fever were observed during the treatment.

Statistical method

SPSS18.0 (Beijing Strong Vinda Information Technology Co., Ltd., China) was used for statistical analysis. GraphPad Prism 7 was used to draw the data image, and the count data was represented by [n (%)]. The chi-square test was used to compare the count data between groups, and the measurement data were expressed as mean ± standard deviation (x± sd). The t-test of independent samples was used to compare the measurement data between groups, and the paired t test was used for comparison before and after the group. $P<0.05$ indicates that the difference is statistically significant.

Results

No significant differences in baseline data between two groups

There were no significant differences in clinical baseline data between group A and group B ($P>0.05$), including gender, age, body mass index (BMI), cause of injury, time of injury to hospitalization, site of injury, ASIA classification, history of smoking, history of drinking, blood glucose (Glu), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) (**Table 1**).

Table 2. Therapeutic effects between group A and group B [n (%)]

Group	n	Significant effect	Effective	Invalid	Total effective rate (%)
Group A	34	20 (58.82)	12 (35.29)	2 (5.88)	94.12
Group B	34	11 (32.35)	13 (38.24)	10 (29.41)	70.59
χ^2 value	-	-	-	-	6.476
P value	-	-	-	-	0.011

Table 3. Neurological ASIA scores before and after treatment in group A and group B ($\bar{x}$±sd)

Group	n	Motor function score		Pain score		Tactile score	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A	34	62.16±9.87	76.91±12.73	73.62±11.46	89.74±13.68	74.51±12.39	92.73±14.42
Group B	34	61.81±10.27	68.37±11.42	74.64±12.08	81.57±12.94	75.83±12.71	83.67±15.92
t value	-	0.143	2.912	0.357	2.530	0.434	2.459
P value	-	0.887	0.005	0.722	0.014	0.666	0.017

Table 4. SAS and SDS scores before and after treatment in group A and group B ($\bar{x}$±sd)

Group	n	SAS score		SDS score	
		Before treatment	After treatment	Before treatment	After treatment
Group A	34	91.53±4.17	71.68±3.95	89.64±4.51	68.75±4.09
Group B	34	90.67±4.31	78.57±3.24	88.37±3.08	75.49±4.28
t value	-	0.406	7.864	1.356	6.639
P value	-	0.836	<0.001	0.180	<0.001

BMSCs transplantation showed higher effective rate compared with conventional therapy

In group A, 20 cases were markedly effective (58.82%), 12 cases (35.29%) were effective, and 2 cases (5.88%) were ineffective after treatment. The effective rate was 94.12%. In group B, 11 cases (32.35%) were markedly effective, 13 cases were effective (38.24%), and 10 cases (29.41%) were ineffective after treatment. The effective rate is 70.59%. The effective rate of group A was significantly higher than that of group B (P<0.05) (**Table 2**).

Group A showed more neurological changes

There were no significant differences in motor, pain and tactile scores between the AIA and the B group before treatment (P>0.05). The motor score, sense of pain score and tactile sense score in the ASIA of group A and group B were significantly higher than those before treatment (P<0.05). The motor score, sense of pain score and tactile sense score in the ASIA of group A after treatment were significantly higher than those of group B (P<0.05) (**Table 3**).

BMSCs transplantation improved bad mood

There was no significant difference in SAS and SDS scores between group A and group B before treatment (P>0.05). The SAS and SDS scores of group A and group B were significantly lower than those before treatment (P<0.05). The SAS and SDS scores of group A after treatment were significantly lower than those of group B (P<0.05) (**Table 4**).

BMSCs transplantation had no adverse reactions

After BMSCs transplantation, 1 patient developed low back pain, 2 patients developed fever, and 1 patient developed headache and did not receive special treatment. The symptoms disappeared after 1-2 days.

BMSCs transplantation leads to high quality of life

The scores of overall health, physiological function, social function, physical pain, physiological function, vitality, mental health and emo-

Table 5. SF-36 items after treatment in group A and group B ($\bar{x}$±sd)

Project	Group A (n=34)	Group B (n=34)	t value	*P* value
Overall health				
	45.85±7.02	46.42±7.25	0.229	0.743
	61.82±8.16	50.75±8.26	5.559	<0.001
Physiological function				
	55.86±8.13	55.64±8.02	0.112	0.911
	71.51±9.45	62.63±9.08	3.951	<0.001
Social function				
	50.02±7.12	48.35±8.48	0.382	0.879
	64.37±7.43	52.81±6.67	6.751	<0.001
Somatic pain				
	58.15±8.36	58.96±6.35	0.450	0.654
	76.28±6.50	64.57±5.28	8.154	<0.001
Physiological function				
	46.15±7.45	45.34±6.15	0.489	0.627
	63.39±6.01	52.49±5.43	7.847	<0.001
Vitality				
	55.17±7.03	54.56±6.53	0.371	0.712
	69.36±7.54	60.08±7.85	4.971	<0.001
Mental Health				
	59.36±6.27	60.15±7.02	0.489	0.626
	73.28±8.15	64.59±7.34	4.620	<0.001
Emotional function				
	65.05±7.25	66.18±7.11	0.649	0.519
	80.43±7.32	71.43±6.91	5.213	<0.001

tional function in SF-36 of group A were significantly higher than those of group B (P< 0.001) (**Table 5**).

Discussion

SCI is a common disease in clinical surgery and has a high disability rate. It can even cause death when the condition is severe [22]. SCI patients are often accompanied by severe neuronal apoptosis and necrosis, and the body's spinal cord tissue self-repair ability is weak, so the neurological dysfunction caused by injury is difficult to repair [23]. With the deepening of research on SCI, stem cell transplantation has become the most promising treatment for SCI [24]. BMSCs are a kind of stem cells that are easy to transplant, easy to obtain, and have a wide range of functions that regulate the differentiation function. It originates from the body, thus avoiding ethics and immune rejection, and is currently a research hotspot of SCI stem cell transplantation [25].

Previous studies have confirmed the therapeutic effect of BMSCs on SCI. For example, Pu et al [26] showed that thrombospondin-1 modified BMSCs can promote neurite outgrowth and functional recovery in rats with spinal cord injury. Also, Wang et al [27] confirmed that the SDF-1/CXCR4 axis can promote the recovery of SCI by mediating BMSCs. In previous studies, the treatment of BCIs with SCI was mostly concentrated in vitro, but there were few studies on specific applications in the clinic. In this study, SCI patients were treated with autologous BMSCs via subarachnoid injection, combined with systematic rehabilitation training. The results showed that the effective rate of group A was significantly higher than that of group B. After treatment, the motor function, pain and tactile scores of group A were significantly higher than those of group B. The symptoms and signs of patients with SCI were improved to different extents. We hypothesize that the reason why BMSCs can produce therapeutic effects in patients with SCI may be due to the local accumulation, integration and migration of BMSCs to SCI after survival. BMSCs can continuously rebuild spinal cord tissue by secreting neurotrophic factors and supplementing endothelial cells. BMSCs secrete neurotrophic factors and supplement endothelial cells, enabling continuous reconstruction of spinal cord tissue, thereby reducing necrosis around the spinal cord and avoiding cell re-injury. Liu et al [28] showed that the umbilical cord mesenchymal stem cell (UC-MSCs) significantly improved the pain sense, tactile sense, movement and daily activities of patients with SCI, which is similar to our study. Both UC-MSCs and BMSCs are a kind of mesenchymal stem cells, which have certain similarities in biological functions [29].

Most patients with SCI have motor and sensory dysfunction, accompanied by varying degrees of self-care and excretion, which have a serious impact on the patient's psychological and life quality [30]. Related studies have shown that severe depression is the most common mental illness associated with SCI, accounting for approximately 25-30% of SCI patients [31]. In

addition, Craig et al [32] showed that SCI can have a significant negative impact on the patient's mental state, and patients will have psychological barriers. The SAS and SDS scores of group A and group B after treatment were significantly lower than those before treatment, and the scores of SAS and SDS in group A were significantly lower than those in group B after treatment. The life quality of the patient after 6 months of discharge was further investigated. The results showed that the overall health, physiological function, social function, physical pain, physiological function, vitality, mental health and emotional function scores of the SF-36 items in group A were significantly higher than those in group B. This indicates that the patient's adverse mood and life quality can be significantly improved after treatment with BMSCs. This may be because after the treatment, the patient's symptoms are obviously improved, the self-care ability and the activity ability of daily life are improved, and the psychological and life quality of the patient are obviously improved. Therefore, BMSCs transplantation may be an ideal treatment for SCI.

This study confirmed that BMSCs transplantation has a better therapeutic effect on SCI. However, the clinical application of BMSCs in SCI is still in its preliminary stage. Therefore, the mechanism has not been further explored, and the best clinical transplantation method of BMSCs remains to be further discussed. This study did not conduct long-term follow-up of SCI patients. The effect on long-term patients is not clear, so there are certain deficiencies. These deficiencies need to be further supplemented in future research, and further evidence will be provided for the conclusions of this study.

In summary, BMSCs transplantation has a good therapeutic effect on SCI. It can promote the recovery of neurological function in patients, can alleviate the patient's bad mood and improve the quality of life, with fewer adverse reactions, which may be an ideal treatment for SCI.

Disclosure of conflict of interest

None.

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