Original

Bone Marrow Mesenchymal Stem Cells Transplantation on Acute Spinal Cord Injury

Hua Song1,2, Shiqi Suo3, Chao Ning4, Yang Zhang5, Weidong Mu5 and Song Chen4

1 School of Medicine, Shandong University, Jinan, Shandong Province, China
2 Department of Orthopaedics, Tengzhou Central People’s Hospital, Tengzhou, Shandong Province, China
3 Department of Gynecology, Affiliated Hospital of Hebei University of Engineering, Handan, Hebei Province, China
4 Department of Orthopedics, Affiliated Hospital of Hebei University of Engineering, Handan, Hebei Province, China
5 Department of Orthopaedics, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong Province, China

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Abstract: To investigate the clinical efficacy of autologous bone marrow mesenchymal stem cells transplantation in patients with acute spinal cord injury. The clinical manifestations of these patients are abnormal sensation and motor functions that dominated by damaged nerve segment. A total of 36 patients with acute spinal cord injury were randomly divided into control group (n=18, treated with decompression + internal fixation + conventional medical treatments) and experimental group (n=18, control group’s treatment + autologous bone marrow mesenchymal stem cells injection in the subarachnoid space). The total effective rate in the observation group was higher than control group (P=0.045). After 12 months of treatment, the SCIM-III score, ASIA exercise score, Botsford score, and ASIA sensory score were significantly higher than those before treatment in both groups, and the increase in the observation group was more obvious (P<0.05). The time for muscle strength and muscle function recovery and independent walking in the observation group were less than those of the control group (P<0.05). Autologous bone marrow mesenchymal stem cells transplantation can improve the therapeutic effect and nerve function, promote the recovery of motor function, sensory function and spinal cord injury without disorder in humoral immune function.

Key words: Acute spinal cord injury, Autologous bone marrow mesenchymal stem cells transplantation, Neural function, Recovery time, Safety

Introduction

Acute spinal cord injury is a multiple neurosurgical disorder, which was caused mechanical damage on the spinal cord induced by the compression of high-explosive and high-energy trauma-induced fracture fragments or displaced vertebral bodies on the spinal canal1-4. The clinical manifestations of these patients are abnormal sensation and motor functions that dominated by damaged nerve segments, and the prognosis is poor5-7. There is a risk of cascade reaction in molecular level. In the past, acute spinal cord injury was treated with fixed surgery, but the postoperative spinal sensation and motor dysfunction were still intractable8-9. Therefore, it is urgent to find new treatment methods since the traditional treatment is not effective enough.

Bone marrow mesenchymal stem cells (BMSCs) could differentiate into neural cells and play an important role in bone marrow hematopoiesis and structural support. Recently, the research on BMSCs has developed a lot and the repairing effect of BMSCs on spinal cord function has been confirmed in clinic10,11. Both animal experiments and clinical studies have proved that BMSCs transplantation has a good effect in the treatment of spinal cord injury repair. This may be related to the differentiation ability of BMSCs into neurons and nerve cells after transplantation, which could promote the endogenous repair reaction at the injury site, reduce the local inflammatory response, promote the repair of damaged demyelinated cells, and reconstruct synaptic connections. Meng et al. and other studies found that administrating BMSCs which pre-treated with hypoxia to rats with acute spinal cord injury significantly enhanced the proliferation of microglia and improved the recovery of neurological function. However, there are few reports on the transplantation of BMSCs in patients with acute spinal cord injury. Therefore, herein, relevant cases were selected to explore the effect of autologous BMSCs transplantation on acute spinal cord injury in clinic.

Materials and Methods

Patients selection

Thirty-six patients admitted in Affiliated Hospital of Hebei University of Engineering from February 2017 to February 2018 were enrolled in this study, all of which were diagnosed as acute spinal cord injury according to CNS/AANS Acute Cervical and Spinal Cord Injury Management Guide (2013). These patients were divided into the experimental group and control group (both n=18) according to the random number table method. In the experimental group, there were 12 males and 6 females, aged between 19 and 59 years old, with an average of 41.2±2.3 years; in the control group, there were 10 males and 8 females aged between 21 and 27 years with an average of 41.7±2.1 years. There was no significant difference in sex ratio and mean age between the two groups (P>0.05). This study has been approved by the Ethics Committee of Affiliated Hospital of Hebei University of Engineering (Approval number: No. 2016120101) and informed consent was obtained from participants.
Inclusion and exclusion criteria

Inclusion criteria: Patients met the above diagnostic criteria; patients aged between 19-60 years old; patients received decompression and internal fixation 72 h after trauma; patients had signed the informed consent

Exclusion criteria: Patients had mental disorder; patients had severe cardio-pulmonary vascular disease; patients had abnormal coagulation function; patients had internal haemorrhage; patients who were allergic to drugs used in this study.

Therapeutic schedule

All patients were admitted to the hospital within 24 h after the injury, and were given a reduction, fixation and decompression on spinal canal within 48 h of the injury. On this basis, patients in the control group were given hemostatic agents, hormone for anti-inflammatory, dehydrating agents, antibacterial drugs, anti-infective and neurotrophy drugs.

In the experimental group, patients were given subarachnoid injection of autologous BMSCs on the basis of treatments in the control group. The operation was as follows: the routine bone marrow puncture was performed on anterior superior iliac spine with 3 points on each side, to extract a total of 120-180 ml bone marrow blood with 20-30 ml on each point. The blood was treated with heparin for anticoagulation and stored at low temperature for later use.

Then the stem cells were separated out, purified and cultured. Briefly, glacial acetic acid (Jinan Kunfeng Chemical Co., Ltd., Jinan, China) were added into the blood to remove red blood cells and the blood clot were removed by filtration, and the upper fat droplets was cleaned by washing with PBS solution. Then the DMEM/F12 (Gibco, California, USA) containing autologous serum was added (1:1, v/v), and then the mixture was added onto the surface of Percoll (Phamacia Corporation, USA, 1.5:1, v/v) followed by centrifugation (TDL-40B desktop centrifuge, Shanghai Anting Scientific Instrument Factory, Shanghai, China) at 2,500 rpm for 30 min to obtain mononuclear cells. The cells were seeded at a density of $2 \times 10^5/\text{cm}^2$ in a culture flask (Gibco, California, USA) for routine culture for 3-4 days, and then the medium was changed. Stem cells with the quantity of $1.0 \times 10^7$ could use for transplantation therapy.

After successful puncture on the patient’s lumbar, the needle core was pulled out and 5 ml of cerebrospinal fluid was extracted. Then 10 ml of prepared autologous bone marrow stem cells were slowly injected into the subarachnoid space. After the treatment, the puncture needle was inserted and the puncture needle was slowly taken out. Another transplantation was performed 5 days later. After transplantation, the patients should keep supine position and their vital signs such as blood pressure, respiration, pulse and heart rate should be closely monitored.

Observation indicators

Main outcomes: The therapeutic effect: cure, the symptoms were all disappeared, and the motor and sensory functions were recovered to normal level; markedly effective, the symptoms improved significantly, the complications were controlled effectively; effective, the symptoms were relatively improved; invalid, the symptoms were not significantly changed or even aggravated. Total effective rate (%) = (number of cure cases + number of effective cases + number of effective cases) / total number of cases * 100.

Neurological recovery (four dimensions): Firstly, Independent Scale of Spinal Cord Injury III (SCIM- III) evaluated activities (0-40 points), sphincter and respiratory muscle examination (0-40 points), self-care ability (0-20 points) with a total of 100 points and a higher score indicated a better spinal cord function recovery. Secondly, ASIA exercise score evaluated muscle force of 10 key sarcomere and the unilateral score was up to 50 points, while the both sides up to 200 points. Thirdly, Botsford score evaluated the bladder function (5 points), rectal function (10 points), and sensory function (10 points) with a total score of 25 points; a higher score suggested a more ideal the recovery situation. Finally, ASIA sensory score was evaluated under normal circumstances, with unilateral score was up to 56 points and two sides score was up to 112 points, and the whole-body score was up to 224 points.

Secondary outcomes: (1) Immunoglobulin levels: 4 ml of fasting venous blood before and after treatment was collected and centrifuged at 2,000 xg for 10 min to obtain the serum to detect the IgG, IgA, IgM levels by immunoturbidimetry before and after treatment; (2) CD3$^+$ and CD4$^+$ T lymphocyte levels of patients were detected by using flow cytometry before and after treatment; (3) muscle strength recovery: the myodynamia recovery time, the muscle function recovery time and the time for patients starting independent walking were compared; (4) adverse reaction rate: the adverse reactions including gastrointestinal dysfunction, headache etc. were recorded and analyzed.

Statistical analysis

The experimental test data were accurately recorded and analyzed by SPSS22.0 software. The count data were expressed as percentage and compared by chi-square test. The measurement data were expressed as mean ± standard deviation and analyzed by t test or paired t-test. $P<0.05$ indicates a difference was statistically significant.

Results

General data analysis

The baseline data including gender, age and injury cause and site of the two groups were similar ($P>0.05$) (Table 1).

Comparison of the total effective rate between the two groups

The total effective rate in the experimental group was 94.4%, which was higher than that of the control group (61.1%; $P=0.045$) (Table 2).

Comparison of neurological recovery between the two groups

Before treatment, there were no difference in the neurological function including SCIM-III score, ASIA exercise score, Botsford score, and ASIA sensory score between two groups ($P>0.05$). After 12 months of treatment, these scores were higher than before treatment in both groups and the increase in the experimental group was significantly higher than that in the control group (all $P<0.05$) (Table 3 and Fig. 1).

Comparison of immunoglobulin levels between the two groups

There was no significant difference in IgG, IgA and IgM levels between the two groups ($P>0.05$). After the treatment, there was no significant changes in IgG, IgA and IgM levels when compared with those before treatment and there was no significant difference between the two groups ($P>0.05$) (Table 4 and Fig. 2).

Comparison of $T$ lymphocyte levels between the two groups

Before treatment, there was no difference in CD3$^+$ and CD4$^+$ T lymphocyte subsets between the two groups ($P>0.05$), which were decreased in both groups after treatment ($P<0.05$). There was no significant difference between the two groups after treatment ($P>0.05$) (Table 5 and Fig. 3).
Table 1. Comparison of baseline data between the two groups

| Groups                  | Experimental group (n=18) | Control group (n=18) | χ²/t  | P   |
|-------------------------|---------------------------|----------------------|-------|-----|
| Gender (n)              |                           |                      | 0.468 | 0.494|
| Male                    | 12                        | 10                   |       |     |
| Female                  | 6                         | 8                    |       |     |
| Average age (years)     | 41.2±2.3                  | 41.7±2.1             | 0.681 | 0.5 |
| Injury cause (n)        |                           |                      | 0.237 | 0.888|
| Trauma                  | 13                        | 14                   |       |     |
| Cervical spondylotic myelopathy | 3          | 2                    |       |     |
| Tethered cord syndrome | 2                         | 2                    |       |     |
| Injury site (n)         |                           |                      | 1.364 | 0.85|
| Cervical cord           | 9                         | 10                   |       |     |
| Thoracic cord           | 4                         | 5                    |       |     |
| Lumbar cord             | 3                         | 2                    |       |     |
| Cervical and thoracic cord | 1             | 1                    |       |     |
| Thoracic and lumbar cord | 1                        | 0                    |       |     |

Table 2. Comparison of the total effective rate between the two groups (n, %)

| Groups                     | Cure                      | Markedly effective | Effective | Invalid | Total effective rate |
|----------------------------|---------------------------|--------------------|-----------|---------|----------------------|
| Experimental group (n=18)  | 9 (50.0)                  | 6 (33.3)           | 2 (11.1)  | 1 (5.6) | 17 (94.4)           |
| Control group (n=18)      | 6 (33.3)                  | 4 (22.2)           | 1 (5.6)   | 7 (38.9)| 11 (61.1)           |
| χ²                        |                           | 4.018              |           |         |         |
| P                         |                           | 0.045              |           |         |         |

Table 3. Comparison of neurological recovery between the two groups (x ± sd)

| Time point                  | Experimental group (n=18) | Control group (n=18) | t     | P   |
|-----------------------------|---------------------------|----------------------|-------|-----|
| SCIM-III score              |                           |                      |       |     |
| Before treatment            | 40.83±6.58                | 41.73±6.34           | 0.418 | 0.679|
| 12 months after treatment   | 72.53±4.31                | 63.52±5.04           | 5.764 | 0   |
| t                           | 17.098                    | 11.414               |       |     |
| P                           | 0                         | 0                    |       |     |
| ASIA exercise score         |                           |                      |       |     |
| Before treatment            | 59.75±5.22                | 59.79±5.18           | 0.023 | 0.982|
| 12 months after treatment   | 81.13±3.81                | 70.89±4.77           | 7.116 | 0   |
| t                           | 14.036                    | 6.688                |       |     |
| P                           | 0                         | 0                    |       |     |
| Botsford score              |                           |                      |       |     |
| Before treatment            | 12.23±2.82                | 12.05±2.79           | 0.193 | 0.848|
| 12 months after treatment   | 22.45±2.13                | 18.07±2.32           | 5.9   | 0   |
| t                           | 12.269                    | 7.039                |       |     |
| P                           | 0                         | 0                    |       |     |
| ASIA sensory score          |                           |                      |       |     |
| Before treatment            | 61.58±5.11                | 61.13±4.28           | 0.286 | 0.776|
| 12 months after treatment   | 80.36±6.49                | 69.21±6.33           | 5.218 | 0   |
| t                           | 9.646                     | 4.486                |       |     |
| P                           | 0                         | 0                    |       |     |
Figure 1. Comparison of neurological recovery between the two groups. (A) SCIM-III score; (B) ASIA exercise score; (C) Botsford score; (D) ASIA sensor score. Compared with before treatment, ***$P$<0.001; compared with the control group, ▲▲▲$P$<0.001.

Table 4. Comparison of immunoglobulin levels between the two groups (x±sd)

| Time point                | Experimental group (n=18) | Control group (n=18) | t     | $P$    |
|---------------------------|---------------------------|----------------------|-------|--------|
| IgG (g/l)                 |                           |                      |       |        |
| Before treatment          | 10.78±4.59                | 10.08±3.77           | 0.5   | 0.62   |
| 12 months after treatment | 9.98±4.62                 | 9.65±3.41            | 0.244 | 0.809  |
| t                         | 0.521                     | 0.359                |       |        |
| $P$                       | 0.604                     | 0.722                |       |        |
| IgA (g/l)                 |                           |                      |       |        |
| Before treatment          | 1.93±0.57                 | 1.89±0.78            | 0.176 | 0.862  |
| 12 months after treatment | 1.83±0.63                 | 1.78±0.41            | 0.282 | 0.779  |
| t                         | 0.499                     | 0.53                 |       |        |
| $P$                       | 0.621                     | 0.6                  |       |        |
| IgM (g/l)                 |                           |                      |       |        |
| Before treatment          | 1.29±0.50                 | 1.27±0.62            | 0.107 | 0.916  |
| 12 months after treatment | 1.32±0.41                 | 1.30±0.34            | 0.159 | 0.874  |
| t                         | 0.197                     | 0.18                 |       |        |
| $P$                       | 0.845                     | 0.858                |       |        |
Table 5. Comparison of T lymphocyte levels between the two groups (M ± sd)

| Time point                  | Experimental group (n=18) | Control group (n=18) | t     | P     |
|-----------------------------|---------------------------|----------------------|-------|-------|
| CD3+ (%)                    |                           |                      |       |       |
| Before treatment            | 81.42±8.01                | 79.64±7.02           | 0.709 | 0.483 |
| 12 months after treatment   | 74.12±6.51                | 75.65±6.53           | 0.704 | 0.486 |
| t                           | 3.001                     | 2.943                |       |       |
| P                           | 0.005                     | 0.004                |       |       |
| CD4+ (%)                    |                           |                      |       |       |
| Before treatment            | 41.87±5.21                | 41.92±5.29           | 0.029 | 0.977 |
| 12 months after treatment   | 39.31±2.24                | 39.65±3.21           | 0.369 | 0.715 |
| t                           | 3.192                     | 2.594                |       |       |
| P                           | 0.002                     | 0.011                |       |       |

Figure 2. Comparison of immunoglobulin levels between the two groups. (A) IgG; (B) IgA; (C) IgM.

Figure 3. Comparison of T lymphocyte levels between the two groups. (A) CD3+ T lymphocytes; (B) CD4+ T lymphocytes. Compared with before treatment, *P<0.05, **P<0.01.
Comparison of muscle strength and function recovery time between the two groups

The time for recovery of muscle strength, recovery of muscle function, and starting independent walking in the experimental group were less than those in the control group (all \( P < 0.01 \)) (Table 6 and Fig. 4).

Comparison of the adverse reaction incidence between the two groups

The total adverse reaction rate in the experimental group was 11.1\%, which was similar with that in the control group (16.7\%, \( P > 0.05 \)) (Table 7).

Discussion

Guo et al. reported that compared with the controls, the sensory score, daily living ability score, shallow sensory score, deep sensory score and motor function score were significant improved in patients with spinal cord injury who were treated with BMSCs transplantation\(^{15}\). In our study, patients with acute spinal cord injury were also received BMSCs transplantation and our results suggested that BMSCs have a good curative effect on acute spinal cord injury and can effectively promote the recovery of nerve function and motor function, which is consistent with the previous literature. The research of Y Dong et al. showed that neurotrophic protein 3 could promote the survival of bone marrow mesenchymal stem cells transplanted to the spinal cord injury area, and potentially enhance the therapeutic effect of repairing spinal cord injury, which is consistent with the literature report\(^{16}\).

The reason for BMSCs can effectively improve spinal cord injury may be related to the following mechanisms. On the one hand, after autologous BMSCs transplantation, stem cells can gradually fuse with the tissue in the lesion and convert to the nerve cell phenotype to replace damaged nerve cells and promote the recovery of nerve circuits and nerve function. On another hand, BMSCs can secrete catecholamines, release brain-derived nerve growth factor, and promote spinal cord injury Gradual integrity. Moreover, BMSCs differentiate to potential endothelial progenitor cells, which can directly participate in the process of injury repair and neurovascular formation, so as to promote the recovery of spinal cord injury\(^{17-18}\). Meanwhile, some scholars have also found that in the early stage of BMSCs secret neurotrophic factors to promote the growth of axons, repairing the damaged spinal cord; while in the late stage, they improve the nerve function mainly through the gradual transformation into neurofunctional cells to replace the damaged host cells\(^{19}\).

In our study, the results also showed that the levels of immunoglob-
ulins in the two groups did not differ before and after treatment, indicating that the transplanted BMSCs would not stimulate the proliferation of immunoglobulin or trigger hypersensitivity and immune response, so it is relatively safe method. Meanwhile, we found that T lymphocytes were decreased in both groups after treatment, however, there was no difference in the degree of decline between the groups, indicating that the BMSCs did not impact the internal environment stability. Furthermore, the adverse reactions rate was insignificantly different between the two groups, suggesting that the BMSCs transplantation can shorten the healing process with high level of safety. Gao et al. also found that after half a year of BMSCs transplantation, the neurological function and living ability were evidently improved without adverse events occurred during follow-up, which is consistent with the results of our study.

However, this is only a preliminary study which has some limitations, such as the small sample size and short observation time, moreover, the long-term efficacy and specific mechanism haven’t investigated. Therefore, a multicenter study with large sample size and long-term follow up are needed in the future, and the specific mechanism would be explored. At the same time, MRI or other images were not used to evaluate the curative effect in this study, which made the research results slightly thin and lack of image demonstration. In the future study, further observation will be made to evaluate the curative effect intuitively.

In summary, autologous bone marrow mesenchymal stem cells transplantation can effectively improve neurological function, promote bladder and rectal function, motor function, sensory function, spinal cord injury recovery in patients with acute spinal cord injury, with or without immune function, shorter recovery time as well as less adverse reactions, which is worth promoting in clinic.

Conflict of Interest
The authors have declared that no COI exists.

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