The Journal of TRAUMA® Injury, Infection, and Critical Care

Spinal Cord Injury Treatment With Intrathecal Autologous Bone Marrow Stromal Cell Transplantation: The First Clinical Trial Case Report

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J Trauma. 2008;64:53–59.

Spinal cord injury often results in devastating dysfunction and disability. When a spinal cord is injured, various symptoms are presented depending on the segments of the damage and the degree. If cervical spinal damage is severe, tetraplegia results. If damage occurs at levels higher than C4, diaphragmatic movement will be impaired, and the patient has to live being connected with the ventilator on the bed. Patients will suffer from acute hyperesthesia or severe chronic pain, urinary and rectal dysfunction, and autonomic dystonia as well as motor and sensory deficits.

In Japan, there are more than 100,000 victims suffering from spinal injury, and a new 5,000 to 6,000 patients are added every year. In the Unites States, about 250,000 to 400,000 people are living with spinal cord injury, and there are about 11,000 to 13,000 new injuries every year. The number of incidence is increasing. The majority of them result from motor vehicle or sports injuries, violence, or falls.[1]

An injured central nervous system never regenerates. This has long been thought as a medical common sense terms. Therefore, the principal object for the treatment of spinal injury was mainly purposed how to minimize the progression of secondary injuries and maintain the remnant function of the spine. For the purpose of preventing secondary spinal cord injury, spine stabilization for the fracture or dislocation and rehabilitation were the main strategy in the treatment.

There has been no successful treatment for the severe spinal cord injury to recover the function satisfactorily.[2] However, if spinal cord damage is functionally improved even at the minimum, it will affect not only the physical, mental, and economic status of patients and their families, but also the medical resources of society. Recently, regenerative treatments with stem cells are in the limelight. However, there are some serious problems such as ethical ones to be solved for the study with stem cells. We reported significant recovery of motor function in rats with experimental spinal cord injury treated by transplanting bone marrow stromal cells (BMSCs) in the cerebrospinal fluid (CSF).[3,4] Based on that study, we aimed at the clinical application of this treatment, and actually planned a clinical trial of spinal cord injury treatment by transplanting patient's autologous BMSCs into CSF in the acute phase after spinal cord injury, at Kansai Medical University Hospital. We have developed a detailed protocol for the clinical trial. The medical ethics committees of the institutions have approved the protocol officially. This clinical trial aims to treat a damaged spinal cord by a novel method of injecting BMSCs into CSF through the lumbar puncture, and assess the safety and efficacy of the procedure. Although we have experienced only a single case, a committee that monitors the data to assess the efficacy and safety of the trial with members independent of this study team has evaluated the safety of the trial in this case, approved to continue the study, and agreed to submit a report of the first case. In addition, Japan Spinal Cord Foundation strongly requested to disclose the course of the first case. Therefore, we would like to publish the report of the first case to enhance research work on the new strategy for the difficult treatment of spinal cord injury.

Submitted for publication July 6, 2007.

Accepted for publication September 18, 2007.

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This work was supported, in part, by a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science, Japan.

Presented in part at the 8th Asian Pacific Conference on Disaster Medicine, November 22, 2006, Tokyo, Japan; at the Shanghai International Conference on Trauma and Emergency Medicine, May 13, 2006, Shanghai, China; and as a poster at the 66th Annual Meeting of the American Association for the Surgery of Trauma, September 27–29, 2007, Las Vegas, Nevada.

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DOI: 10.1097/TA.0b013e31815b847d

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Table 1 Symptoms and Signs at Admission

Consciousness	Clear
Vital signs	
Blood pressure (mm Hg)	131/68
Heart rate (min^{-1})	70
Body temperature (°C)	36.2
Respiratory rate (min^{-1})	18
Arterial blood gas analysis (under O_2 10 L/m with face mask)	
$Paco_2$ (mm Hg)	41.3
Pao_2 (mm Hg)	102
pH	7.390
Base excess (mmol/L)	0.2
HCO_3^- (mmol/L)	24.2
Neurologic examination	
Motor	
C5 (biceps)	3/5 (MMT)
C6 and lower	0/5
Sensory	
C7 and lower	No sensation
Anal sphincter	(−), no sacral sparing
Priapism	(+)
American Spinal Injury Association Impairment Scale	A

MMT, muscle manual test.

CASE REPORT

A 35-year-old man fell down from about 7-m height during a dismantling construction site work in March 2006. He was transported with a complaint of quadriplegia by a ground ambulance to our Emergency and Critical Care Center.

Symptoms and signs at admission are shown in Table 1. Chief complaint was loss of sensation and movement below C5 level. Cervical spine radiograph revealed a fracture-dislocation of C5 on the lateral view (Fig. 1), and computerized axial tomography (Fig. 2A and B) revealed fractured 4th and 5th cervical vertebra. Figure 3 shows the T1- and T2-weighted magnetic resonance imaging (MRI) at admission. T2-weighted image (Fig. 3B) showed a low-intensity area at the level of C5 that was surrounded by high-intensity area. No other injury was found. He was admitted in intensive care unit. His respiration type was abdominal, but he did not need ventilatory assist. He remained on methylprednisolone protocol, and was administered a single bolus injection of 30 mg/kg methylprednisolone within 8 hours after injury followed by a continuous administration of 5.4 mg/kg/h for 23 hours according to the National Acute Spinal Cord Injury Study II.[5] On the day of admission, he underwent installation of halo brace to prevent secondary injury caused by instability of the cervical spine. His neurologic function was evaluated according to the American Spinal Injury Association (ASIA) Scoring for Standard Neurologic Classification of Spinal Cord Injury (SNCSCI) as shown in Table 2.

As his case was indicated to the clinical trial, we informed his wife about the clinical trial spending several hours while the patient was sedated. Although we informed her of the whole process of the clinical trial, we intended to get the written consent from her in two steps. The first consent was only with collecting bone marrow during the operation for cervical stabilization, and to culture and multiply stromal cells. The first consent should be obtained before operation shortly after the injury occurs, but in this case the patient was sedated and his family was upset, and so we obtained a written consent not with the clinical trial but with only obtaining bone marrow for culture during the operation. The patient and family members could have their time for about a week to discuss whether they would accept the clinical trial, the BMSCs transplantation.

Fig. 1. *Cervical spine radiograph lateral view showed a fracture-dislocation of C5 at admission.*

On day 3, the patient underwent anterior cervical stabilization of C4 through C6 with bone graft and instrumentation. Iliac bone pieces were obtained for grafting to the fractured spine. Simultaneously, cancellous bone of the ilium was collected. Postoperative cervical spine lateral view shows anterior cervical stabilization at C4 through C6 by instrumentation, with spinal canal space at C5 level being opened and maintained (Fig. 4). He needed ventilatory support for a few days after the operation. Rehabilitation pro-

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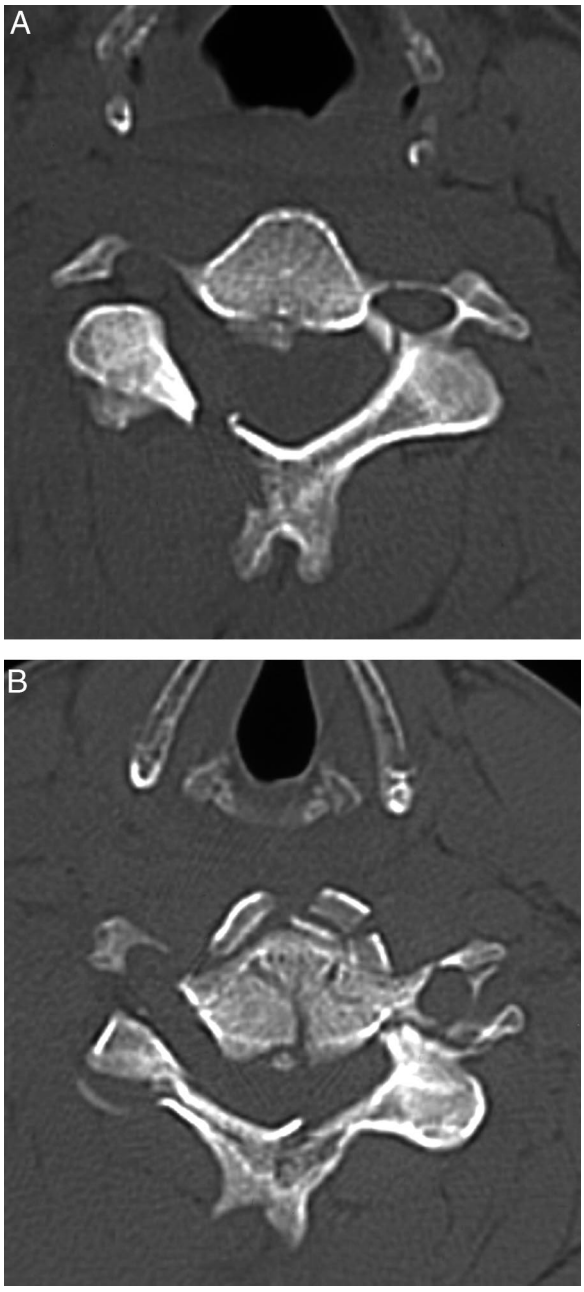

Fig. 2. *Computed tomography at admission revealed the fractured 4th (*A*) and 5th (*B*) cervical vertebra.*

Fig. 3. *MRI at admission. T1-weighted image (*A*) showed no remarkable change, but T2-weighted image (*B*) showed a low-intensity area at the level of C5 that was surrounded by high-intensity area.*

gram was started shortly after the operation similarly for those with conventional treatment.

The cancellous bone was transported to a facility that meets the guideline for Good Manufacturing Practice of cell culture for clinical treatment in Japan, to isolate and culture stromal cells. Stromal cells were multiplied reaching a cell density of 10^6 after 10 days. We discussed again with his wife and the patient himself on the clinical trial at that point. He and his wife were willing to accept the cell transplantation therapy. On day 13, under written consent, 3.1×10^7 BMSCs, suspended in about 2 mL of saline, was transplanted into CSF through lumbar puncture technique. After transplantation, he had no sign of meningitis, such as fever or headache. His clinical course after the transplantation was uneventful and he left intensive care unit 22 days after the transplantation. A few weeks later, he once suffered from

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Table 2 American Spinal Injury Association Scoring for Standard Neurologic Classification of Spinal Cord Injury

	Score			
	Motor	Pinprick	Light Touch	ASIA Impairment Scale
Normal (full)	100	112	112	E
Admission	6	16	16	A
Operation	8	20	17	A
1 mo	10	37	36	A
3 mo	16	34	43	A
6 mo	17	33	36	A

ASIA, American Spinal Injury Association.

Fig. 4. *Cervical spine lateral view after the operation shows anterior cervical fusion at C4 through C6 by instrumentation, with spinal canal space at C5 level being opened and maintained.*

urinary tract infection but no undesirable side effect of cell transplantation was observed throughout his course.

At 1, 3, and 6 months after the transplantation, neurologic function was evaluated in detail according to the SNCSCI of ASIA (Table 2). Motor and sensory scores gradually but apparently improved at 1 and 3 months compared with the scores before the transplantation. MRI at 3 months revealed a cavitation in the spinal cord (Fig. 5). Slight improvement was added to motor score, but no further improvement in the sensory score was observed at 6 months compared with that at 3 months. Changes in the score of key muscles at 6 months are shown in

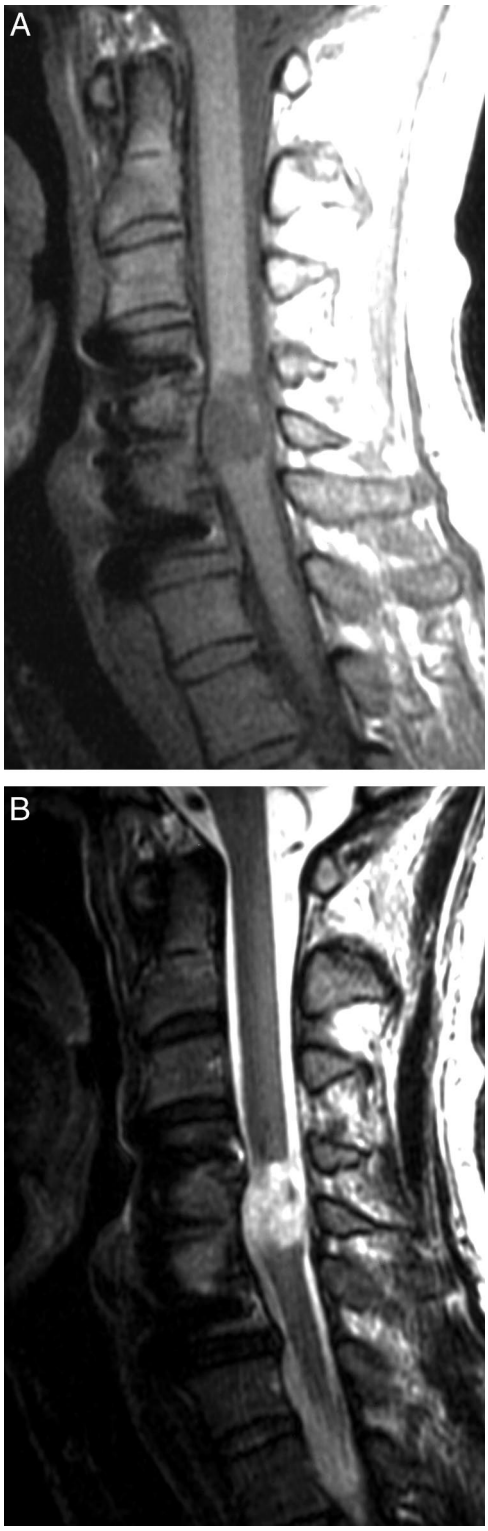

Fig. 5. *Both T1-(*A*) and T2-weighted images (*B*) at 3 months after the transplantation shows a cavity formation at C5 level in the spinal cord.*

Table 3. In addition to the gain in strength in the elbow flexors (C5), the gain in wrist extensors (C6) and elbow extensors (C7) motor levels elevated the motor score in the SNCSCI of ASIA.

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Table 3 Changes in Key Muscles Motor Score

Level	Muscles	Motor Score			
		Before		6 M	
		R	L	R	L
C5	Elbow flexors	3	3	4	4
C6	Wrist extensors	0	0	0	3
C7	Elbow extensors	0	0	3	3
C8	Finger flexors	0	0	0	0

In the protocol of this clinical trial, our main endpoint is to evaluate the changes in motor scores at 6 months, and secondary endpoints are to evaluate the changes in sensory scores, anal functions, and ASIA impairment scale at 6 months. Our protocol does not call for quality of life as a main endpoint. However, we are continuing to observe his quality of life after the 6-month period. He is becoming able to sit on a wheelchair and drive slowly the wheelchair by himself. Further improvement in the scores and quality of life will be reported in our future study at a later time point.

In this clinical trial, patient data were registered and managed by an independent data center for the clinical trial. The efficacy and safety of the study should be discussed and evaluated in a committee with members outside of the study team. By far, the committee has evaluated the efficacy and safety of cell transplantation therapy in this first case. Although definite improvement in the score is obtained, we continue trials and increase the number of applied cases so that the efficacy and safety of this cell transplantation study can finally be evaluated in the committee.

DISCUSSION

Complete recovery of injured spinal cord is still a dream. It has long been thought that damaged central nervous system is fundamentally not recovered. It was reported from Vancouver Hospital that among 70 patients with complete spinal injury for minimum of 2-year complete follow-up, motor recovery did not occur below the zone of injury, although varying degrees of recovery can be expected within the zone of partial preservation.[6] In the study of National Spinal Cord Injury Statistical Center, Alabama, only 5.6% of the 987 subjects with complete motor and sensory paralysis (ASIA grade A) at 1 year recovered to incomplete sensory or incomplete motor function at 5-year evaluation (ASIA grade B, C, or D).[2] Therefore, treatments for victims of spinal cord injury have been focused on preventing secondary damage and maintaining or maximally restoring preserved function by daily rehabilitation. Recently, various experimental or clinical studies with bioactive agents, growth factors, or cellular approaches are going on to inhibit inflammatory and degenerative responses or to enhance neural regeneration.[7–14] Among them, clinical trials and animal experiments using stem cells,[15–17] macrophages,[18] olfactory ensheathing cells,[2,19–23] and BMSCs[24–26] are attracting a great deal of attention.

Among the cells, the BMSCs are of autologous origin and easy to obtain at the operation, and their incubation technique has been established. There will be no immunologic reaction, no ethical problem, and no uncontrollable proliferation as in the case of embryonic stem cells. BMSCs are considered to be realistic to use for the purpose of spinal cord injury treatment.

BMSCs make up approximately 0.125% of the total marrow cells.[27] BMSCs differentiate into osteoblasts, chondrocytes, adipocytes,[28,29] skeletal muscle fibers,[30] cardiomyocytes,[31] hepatocytes,[32] and epithelial cells of liver, lung, intestinal tract, and skin.[33] BMSCs are reported to be capable of differentiating into Schwann cells in culture, and therefore would stimulate peripheral nerve regeneration.[34]

Previously we investigated function of neurospheres derived from hippocampus or spinal cord cells in vitro and in vivo.[35,36] We studied effects of transplantation of neurospheres in rats with Th8–9 level spinal cord contusion made using a New York University weight-drop device.[35] Considering clinical application, it is difficult to use neurosphere cells or neural stem cells from the standpoint of ethical problems. We, therefore, shifted to the study of BMSCs. In vitro, BMSCs exerted profound effects on neurite extension of co-cultured neurosphere cells, suggesting that BMSCs might have some potential regenerating influences to the spinal cord injury.[36] To avoid secondary injury on dissecting and injecting cells in the injured spinal cord, we administered BMSCs into CSF.[37,38] We confirmed significant effects of BMSCs on the improvement of gait by using the open-field Basso, Beattie, and Bresnahan (BBB) scoring system[39] compared with control rats for up to 4 to 5 weeks.[4] In this study, the cavity sizes were significantly smaller in the rats transplanted with BMSCs compared with those without BMSCs.[3,4] After grafting, BMSCs were transported to the site of injury, attached to the injured neural tissue, then gradually decreased in number and disappeared within 3 weeks, promoting tissue repair in the injured spinal cord. This suggests that some trophic factors might be released from BMSCs to rescue neurons and glial cells from degeneration after the crush injury as well as to stimulate differentiation of neural stem cells in the recipient spinal cord.

On the basis of a series of in vitro and in vivo experiments, we planned a clinical trial of spinal cord injury treatment with a novel method. In this trial, only the patients who need operation for the spine stabilization are indicated. BMSCs can be obtained when iliac crest is harvested for grafting. No additional operation is necessary to obtain BMSCs. Multiplied BMSCs were transplanted into CSF by lumbar puncture technique. Therefore, reoperation is not necessary to open and dissect the lesion of the spinal cord as is needed for the direct cell infusion operation into spinal cord. Hence, secondary injury to the spinal cord can be avoided.

We made a protocol to transplant cells within 3 weeks after the injury. It is desired that cell transplantation can be

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Table 4 Eligibility Criteria for the Preliminary Registration

1. Spinal cord injury is confirmed with MRI
2. ASIA Impairment Scale is A, B, or C
3. ISCSCI motor function score can be evaluated
4. Methylprednisolone therapy according to the NASCIS II study can be started within 8 h after the injury
5. BMSCs incubation can be started within 72 h after the injury
6. Age between 15 and 60
7. With the first informed consent of obtaining bone marrow

ASIA, American Spinal Injury Association (ASIA Impairment Scale: A, no motor or sensory function preserved in sacral segments; B, sensory but not motor function preserved in at least sacral segments; C, motor function preserved below the neurologic level and the majority of key muscle have motor score <3); ISCSCI, International Standard Classification of Spinal Cord Injury; NASCIS, National Acute Spinal Cord Injury Study; BMSC, bone marrow stromal cell.

Table 5 Exclusion Criteria

1. Complete disruption of spinal cord
2. Central spinal cord injury
3. Spinal canal stenosis before the injury
4. Brain or spinal cord disease before the injury
5. Multiple organ disease of SOFA score ≥ 12
6. Multiple trauma victim with injuries AIS ≥ 4 in more than 2 segments except for the spinal injury
7. Positive serologic test in at least one of the following; HBs antigen, HCV antibody, HIV antibody, or HTLV-1 antibody
8. Pregnancy

SOFA, sepsis-related organ failure assessment; AIS, Abbreviated Injury Score; HBs, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV, human T-cell leukemia virus.

performed as soon as possible after injury. However, BMSCs take about 7 to 10 days to proliferate to the cell density sufficient for transplantation. Based on the discussion for more than a year about the design of the clinical trial, we made the detailed protocol, which has been approved by the Ethics Review Board of our institutions.

In our protocol, candidates for the trial have to satisfy all the inclusion criteria listed in Table 4, and have no exclusion criteria listed in Table 5. They must be registered to an independent data center before the trial and checked again whether they meet all the inclusion and exclusion criteria. They also have to meet the eligibility criteria (Table 6) before transplantation. In this protocol, those with central spinal cord injury were omitted because they often recover spontaneously. Those with spinal canal stenosis before the injury for reasons such as ossification of posterior longitudinal ligament were also omitted because of a difficulty in evaluation.

Table 6 Eligibility Criteria for the Actual Registration

1. BMSCs $>10^6$ are obtained by the incubation
2. Transplantation can be performed <3 wk after the injury
3. ASIA impairment scale A, B, or C is confirmed within 3 d before transplantation
4. With second informed consent for transplantation

In the study patient, although the findings of MRI (Fig. 3) after the injury suggest a poor prognosis of neural functional recovery, definite improvements were shown in motor and sensory functions up to 6 months. Although this clinical trial study has just started and this report is about only a single case, the safety of injecting autologous BMSCs into CSF has been confirmed in this first clinical case. The efficacy of this kind of cell transplantation should be evaluated by a committee with members outside this study team after a series of cases in accordance with the protocol.

In conclusion, to our knowledge, this is the first report of clinical trial for spinal cord injury treatment by transplanting BMSCs into CSF. As autologous BMSCs are used in our study, no ethical and immunologic problems develop. We are carefully observing the course of the present case. There is no adverse effect that might be caused by the administration of BMSCs into CSF. We have to accumulate in a number of cases so that the effectiveness and safety of BMSC transplantation through CSF can be evaluated on the more secured base in a committee.

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