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Clinical analysis of the treatment of spinal cord injury with umbilical cord mesenchymal stem cells

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Abstract

Background aims. The purpose of this study was to observe the clinical effect and safety of umbilical cord mesenchymal stem cells (UC-MSCs) in treating spinal cord injury (SCI) by intrathecal injection. *Methods.* From January 2008 to October 2010, we treated 22 patients with SCI with UC-MSCs by intrathecal injection; dosage was 1×10^6 cells/kg body weight once a week given four times as a course. Four patients received two courses, one patient received three courses and all other patients received one course. American Spinal Injury Association scoring system and International Association of Neurorestoratology Spinal Cord Injury Functional Rating Scale were used to evaluate neural function and ability to perform activities of daily living. *Results.* Treatment was effective in 13 of 22 patients; nine patients had no response. Among patients with incomplete SCI, the response to treatment was 81.25%; there was no response to treatment among six patients with complete SCI. Five patients with a response to treatment received two to three courses of therapy, and effects in these patients were further enhanced. In most patients in whom treatment was effective, motor or sensory functions, or both, were improved, and bowel and bladder control ability was improved. In 22 patients 1 month after therapy, algesia, tactile sensation, motion and activity of daily living scale were significantly improved ($P < 0.01$). During therapy, common adverse effects were headache (one case) and low back pain (one cases); these disappeared within 1–3 days. No treatment-related adverse events occurred during a follow-up period ranging from 3 months to 3 years. *Conclusions.* UC-MSC therapy by intrathecal injection is safe and can improve neurologic function and quality of life in most patients with incomplete SCI.

Key Words: *spinal cord injury, umbilical cord mesenchymal stem cells*

Introduction

Spinal cord injury (SCI) is a serious injury of the nervous system that can lead to paralysis and urinary and fecal incontinence. Several factors are thought to contribute to the lack of regeneration of spinal cord axons, including a reduction in the intrinsic growth capacity of adult central nervous system projection neurons, the presence of inhibitory cues derived from damaged central nervous system myelin, the formation of a glial scar by local astrocytes in response to inflammatory stimuli and the absence of neurotrophic factors and nerve growth factors. Neither medical nor physical therapy has shown a curative effect.

Many animal studies have shown that mesenchymal stem cells (MSCs) can promote the restoration of neurons. Investigators injected MSCs into the subarachnoid space of rats with spinal injury and found more MSCs in injury parts. Some MSCs can differentiate into neurons and neuroglial cells and promote the restoration of spinal injury (1,2). Yang *et al.* (3) transplanted human umbilical cord mesenchymal stem cells (UC-MSCs) into the lesion site of the rats with complete spinal cord transection. Significant improvements in locomotion were observed that were accompanied by increased numbers of regenerated axons in the corticospinal tract and neurofilament-positive fibers around the lesion site. Hypotheses as to why the MSCs can pass through the cerebrospinal fluid-brain barrier are as follows: (i) Various inflammatory factors and vasoactive substances are released after SCI, which can increase the permeability of the cerebrospinal fluid-brain barrier; (ii) MSCs have a chemotactic response to the injured parts of the spinal cord. Besides directly replacing damaged oligodendrocytes and neurons, MSCs could play an important supportive role in SCI therapies. They could create a more favorable environment for limiting damage and promoting regeneration, via immunoregulation, expression of

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growth factors and cytokines and improved vascularization, providing a permissive growth substrate or suppressing cavity formation, or both (4–6). These different mechanisms are not mutually exclusive, and numerous mechanisms could contribute to improved outcomes.

MSCs can be isolated from bone marrow (BM), umbilical cord (UC) and UC blood. The frequency of MSCs obtained from BM aspirates is about $\leq$0.01%. BM aspiration and *ex vivo* expansion of MSCs for about 3 weeks are needed to obtain MSCs from BM. Crucial points to isolate MSCs from UC blood are a time from collection to isolation, a net volume of UC blood and a mononuclear cell count. In 2003, Mitchell *et al.* (7) first identified MSCs from human UC Wharton's jelly. It was reported that human UC-MSCs have greater *ex vivo* expansion capabilities, faster proliferation and lower immunogenicity than bone marrow mesenchymal stem cells (BM-MSCs) (8,9). Human UC-MSCs can be induced to differentiate *in vitro* into bone, cartilage, adipose tissue (10,11), skeletal muscle cells (12), cardiomyocytes (13,14), endothelium (15) and especially neural cells (7,16–18). The cells possess a potential therapeutic role for treating patients with neurodegenerative diseases and central nervous system injuries. Shetty *et al.* (19) compared the MSCs from BM, UC and UC blood and found these cells all expressed CD73, CD105, SSEA4, CD29, CD44 and HLA-A, HLA-B and HLA-C. UC-MSCs and UC blood MSCs did not express HLA-DR associated with transplant rejection and could maintain the capacity of multilineage differentiation during *in vitro* culture. We used UC-MSCs in the present study. In this study, we observed the therapeutic effect of cell therapy with UC-MSCs by intrathecal injection in 22 patients with SCI.

Methods

Patients

We recruited 22 patients (17 men and five women, average age 33 years) with SCI at our hospital from January 2008 to October 2010. Four patients had cervical cord injuries, two patients had cervical cord and thoracic cord injuries, seven patients had thoracic cord injuries, two patients had thoracic cord and lumbar cord injuries and seven patients had lumbar cord injuries. The average time from injury to participation in the study was 56 months (range, 2–204 months). The causes of injury included motor vehicle accident (eight cases), a fall from a height (eight cases), a crush injury (2), diving accident (two cases), tethered cord syndrome (one case) and sequela of myelitis (one case). The risk of therapy with MSCs (e.g., fever, lumbago, headache, dizziness, suppressed cellular immunity, cerebral embolism, tumor, spasticity, neuropathic pain, possible loss of neurologic function) was explained to the patients, and informed consents were signed. The therapeutic regimen was approved by hospital Ethics Committee and Technology Committee. Before receiving MSC therapy, patients underwent a comprehensive evaluation including physical examination, electrocardiogram, magnetic resonance imaging of the spinal cord, complete blood count, biochemistry and hemostasis tests. No fever or infection was present in any of the patients, and all patients had normal function of the heart, lung, liver, kidney and hematologic system.

UC-MSC preparation

All parts of this study, especially the isolation of the human UC, were performed according to the Declaration of Helsinki. Ethical approval was obtained from the General Hospital of Air Force (Beijing, China), and written informed consent was obtained from UC donors. UC-MSCs were uniformly cultured in the Stem Cell Center of Air Force General Hospital. Cells from different UCs were sampled for immunophenotypic analysis and differentiation assays. MSC preparation was performed as previously reported (7). Briefly, UCs were collected after obtaining signed written informed consent and microbiologic detection. Each human UC was collected from full-term cesarean section births and processed within 3–6 h. Umbilical arteries and veins were removed, and the remaining tissue was diced into small fragments. Equal volume of 0.2% collagenase I was added, and the digestion was carried out at 37°C overnight. The next day, double volume of 0.05% trypsin was added and maintained for 1 h at 37°C. Cells were collected by centrifugation at 2000 rpm for 10 min. Viable cells were counted, suspended in human MSC serum-free culture media (HangZhou Biowish Bio-tech Co., HangZhou, China) and seeded into culture plastic flasks. A few colonies were formed after 7 days, and sub-cultivation was performed. The cells were passaged, and cells at passage 3 (about 21 days of culture) were used for therapy after phenotypic analysis with fluorescence-activated cell sorter (FACSCalibur flow cytometer; BD Biosciences, Franklin Lakes, NJ USA) and differentiation assays (Figures 1 and 2). Bacterial and fungal cultivation of the medium was performed 48 h before cell harvesting.

Clinical use of UC-MSCs

Lumbar punctures were performed after patients were admitted to the hospital. A dosage of 1×10^6/kg

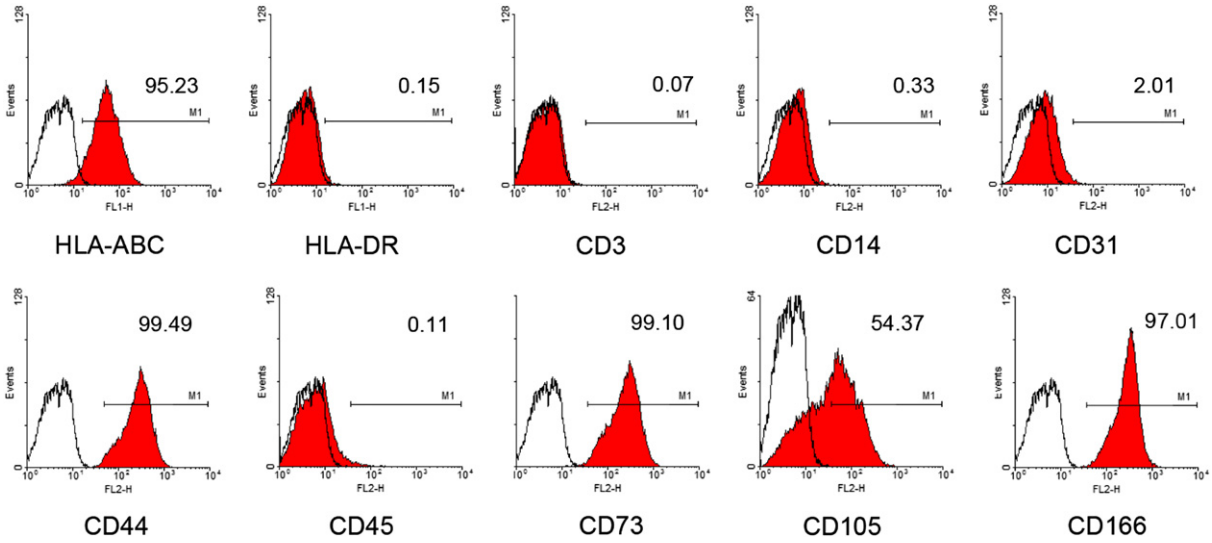

Figure 1. Phenotypic features of UC-MSCs. *y*-axis, events; *x*-axis, relative fluorescence intensity. Positive percentages are indicated.

UC-MSCs (10 mL) with 5 mg of dexamethasome was administered by intrathecal injection weekly four times. Lumbar puncture was performed routinely, 1×10^6/kg UC-MSCs (10 mL) with 5 mg dexamethasome (to prevent aseptic chemical meningitis) was injected into the subarachnoid space and all patients were asked to lie flat without a pillow for at least 6 h to prevent intracranial hypotension syndrome. Each patient received four injections for a total transplantation of 4×10^6/kg UC-MSCs.

Adjunctive therapy

Systemic rehabilitation exercise was performed in the Rehabilitation Department in our hospital. Each patient received individualized physical therapy according to the patient's condition.

Evaluation standard

The International Standards for Neurological Classification of Spinal Cord Injury by the American Spinal Injury Association (ASIA) and International Association of Neurorestoratology Spinal Cord Injury Functional Rating Scale (IANR-SCIFRS) were used by neurologists to evaluate neural function and quality of life of the patients before and immediately after therapy (20). The evaluation was single blind because the neurologists performed the evaluation only and did not participate in the treatment process.

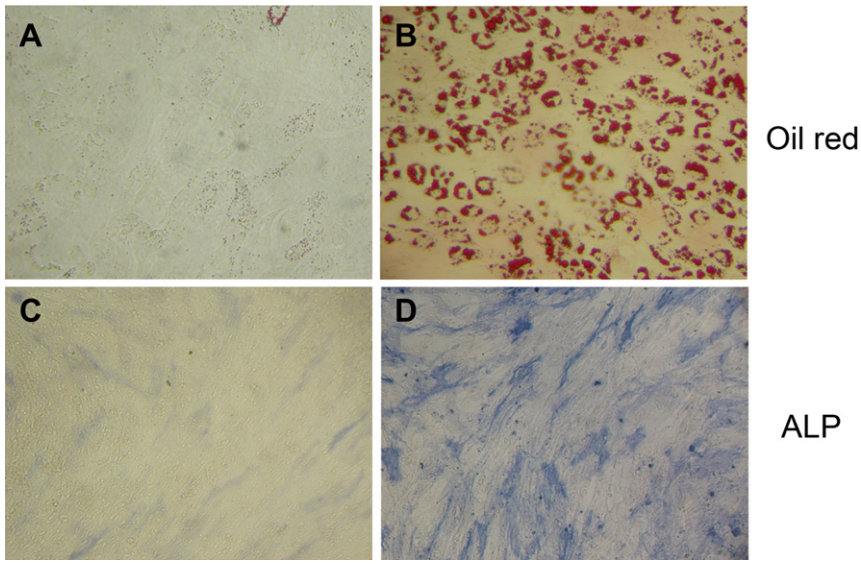

Figure 2. *In vitro* osteogenesis and adipogenesis of UC-MSCs. UC-MSCs were cultured in the absence (A, C) or presence (B, D) of inductive agents for 2 weeks and stained by oil red O for analysis of alkaline phosphatase (ALP) activity.

Table I. Demographic and neurologic characteristics of patients.

Patient no.	Age(y)/ sex	Time from injury (mo)	Level of injury	Therapeutic effect (Y/N)	ASIA score (algesia) before therapy	ASIA score (algesia) after therapy	ASIA score (sensory function) before therapy	ASIA score (sensory function) after therapy	ASIA score (motor function) before therapy	ASIA score (motor function) after therapy	IANR-SCIFRS scores before therapy	IANR-SCIFRS scores after therapy
1	23/F	21	L1	Y	78	88	78	88	54	60	25	37
2	51/M	204	T1-12	Y	106	106	106	106	66	70	36	40
3	48/F	8	L1	Y	104	108	104	108	76	84	45	48
4	48/M	95	T11-12	N	92	92	92	92	106	106	45	45
5[a]	19/F	138	T3-6	N	40	40	40	40	40	40	24	24
6	29/M	12	T1-2	Y	92	92	92	92	80	82	42	43
7[a]	18/M	27	C5-7	N	32	32	32	32	36	36	9	9
8	51/M	52	C4-6	Y	102	112	102	112	79	83	37	41
9	26/M	9	C6-T1	Y	32	36	32	36	36	40	16	20
10[a]	26/M	4	T8	N	56	56	56	56	50	50	21	21
11	39/M	12	L1	Y	80	82	80	82	54	58	28	32
12[a]	32/F	16	T8-10	N	64	64	64	64	50	50	22	23
13	34/M	13	C6-T1	Y	36	48	36	48	46	52	19	27
14[a]	27/M	57	C6	N	66	66	66	66	30	30	16	16
15	20/M	156	Conus medullaris	Y	103	112	103	112	80	87	46	47
16	30/M	11	T12-L1	Y	78	82	78	82	53	56	29	35
17	29/M	18	Conus medullaris	N	102	102	102	102	75	94	44	46
18[a]	36/M	84	C4-6	N	32	32	32	32	10	10	7	7
19	37/M	108	Conus medullaris	Y	72	74	72	74	50	52	35	39
20	31/F	2	T11-L1	Y	70	79	70	81	52	54	24	27
21	30/M	21	L1	N	84	84	84	84	64	64	42	42
22	34/M	162	T12	Y	112	112	—	—	91	95	47	48

F, female; M, male; N, no; Y, yes.
[a]Patients with complete SCI.

Table II. ASIA and IANR-SCIFRS scores of 22 patients before therapy and 1 month after therapy.[a]

Neural function	Before therapy	1 month after therapy	*P*
Motor function	58.1 ± 22.2	61.5 ± 23.9	<0.01
Algesia	73.2 ± 25.1	77.2 ± 26.1	<0.01
Sensory function	74.2 ± 26.7	77.3 ± 26.1	<0.01
Activities of daily living	29.5 ± 12.5	32.7 ± 12.4	<0.01

[a]Sample mean ± standard deviation.

Observation of adverse effects and complications

During a period of 1 month after therapy, fever, lumbago, headache, dizziness and other adverse reactions were observed. If there were no obvious adverse effects, the patients were discharged at 1 month.

Follow-up

Because the patients lived all over China, follow-up was done by telephone. Patients were asked to report regularly to local departments of neurology for a systemic assessment to assess their disease, immune function and MSC-associated adverse effects including tumor. At the time of this writing, the patients were still being followed.

Statistical analysis

Data were analyzed by matching *t* test. *P* values <0.05 were considered statistically significant using a commercially available software package (SPSS, version 11.5 Bizinsight Information Technology Co., Beijing, China).

Results

Clinical symptoms were improved in 13 cases with total effective rate of 59.1%. Of these 13 patients, five patients underwent further treatment with UC-MSCs, and the clinical symptoms were further improved. Improvements in motor function, sensory function and the controllability of defecation were noted (Table I).

The baseline ASIA and IANR-SCIFRS scores were significantly different before and 1 month after treatment. The scores of pain sensation, touch sensation, motor function and activities of daily living were also significantly different before and after treatment ($P < 0.01$) (Table II).

Among 16 patients with incomplete SCI, the clinical symptoms were improved in 13 patients (three cases were deemed ineffective) with the total effective rate 81.25%. The scores of pain sensation, touch sensation, motor function and activities of daily living all were significantly different before and after treatment ($P < 0.01$) (Table III). The six remaining patients with complete SCI all had an ineffective treatment response. Among six patients with myelomalacia in injured parts of the spinal cord, no improvements were observed in five cases. Two of these cases were incomplete SCI, and three cases were complete SCI.

The average time from injury to treatment in 13 patients whose clinical symptoms were improved was 59 months (range, 2−204 months). The average time from injury to treatment in the remaining nine patients whose clinical symptoms were not improved was 51 months (range, 4−136 months). There was no significant difference in the time of injury between these two groups ($P > 0.05$). (Table IV).

Adverse reactions and complications

The vital signs of all patients were stable during UC-MSC therapy. One patient experienced lumbago, and one experienced headache. These symptoms disappeared 1−3 days later without special handling. No fever or other side effects were recorded.

Results of follow-up

All of our patients received MSC therapy in the chronic stage of SCI and were neurologically stable 1 month before cell implantation. Among 13 patients whose clinical symptoms were improved, there were no further improvements in nine patients 1 month after UC-MSC treatment, 3 months after treatment in three patients and 1 year after treatment in one patient. No severe adverse reactions were observed in any of the patients.

Discussion

SCI is a leading cause of disabilities in young adults. Because of the organization of the spinal cord, which

Table III. ASIA scores and IANR-SCIFRS scores of patients with incomplete SCI and complete SCI before therapy and 1 month after therapy.[a]

Type of SCI	n	Time of evaluation	Motor function	Algesia	Sensory function	Activities of daily living
Incomplete SCI	16	Before therapy	66.3 ± 18.5	82.9 ± 21.6	83.9 ± 23.4	35.0 ± 10.2
		1 mo after therapy	71.1 ± 18.5	88.1 ± 21.2	88.2 ± 22.1	38.6 ± 8.2
	P		<0.01	<0.01	<0.01	<0.01
Complete SCI[b]	6	Before therapy	36.0 ± 14.9	48.3 ± 15.6	48.3 ± 15.6	16.5 ± 7.1
		1 mo after therapy	36.0 ± 14.9	48.3 ± 15.6	48.3 ± 15.6	16.5 ± 7.1

[a]Sample mean ± standard deviation.
[b]There was no difference before and after treatment in patients with complete SCI.

Table IV. Time of injury for improve and unimproved patients.

	Improved patients (n = 13)	Unimproved patients (n = 9)	*P*
Time of injury (mo)	59.23 ± 19.96	51.11 ± 15.20	>0.05

transmits ascending sensory information to the brain and descending motor information to the body, injury to the spinal cord has devastating consequences and often results in permanent loss of motor or sensory function, or both, below the site of injury. SCI can be caused by disease and external injury, which accounts for about 90% of SCIs. In this study, 20 patients had SCI caused by external injuries, most of which involved motor vehicle accidents and falls from a height.

Current treatments for SCI include surgery to stabilize the injury site, high doses of corticosteroids to help limit secondary injury processes and rehabilitative care. Although these treatment options may provide benefits, clinical improvements are modest, and many patients still face significant neurologic dysfunction and disability. UC-MSCs are easily obtained from UC and able to expand rapidly *ex vivo*. Studies have shown that MSCs are of low immunogenicity, have mutilineage differentiation capacity and can secrete various bioactive molecules that can promote the reparative process of neural tissues (3,21,22). In addition, there are no ethical issues with the use of MSCs. MSCs have potential efficacy in restoring central lesions.

Studies of MSCs in the treatment of SCI are mostly limited to animal experiments. There are few clinical studies of MSCs in the treatment of SCI. Pal *et al.* (23) transplanted autologous BM-MSCs in 30 patients with SCI via lumbar puncture at a dose of 1×10^6 cells/kg. None of the patients reported any adverse events associated with BM-MSC transplantation in the 3 years of follow-up. A patient who sustained a crush fracture of the L1 vertebral body received stem cell therapy that comprised intrathecal administration of allogeneic UC blood *ex vivo* expanded $CD34^+$ and UC matrix MSCs at 5 months, 8 months and 14 months after injury. Recovery of muscle, bowel and sexual function was noted, and no adverse effects were observed (24).

We applied UC-MSC therapy by intrathecal injection to 22 patients with SCI. The clinical symptoms were improved in 13 patients with total effective rate 59.1%. In 16 patients with incomplete SCI, clinical symptoms were improved in 13 cases (in three cases therapy was deemed ineffective) with a total effective rate 81.25%. The remaining six patients with complete SCI all had an ineffective treatment response. The improvement was limited in six patients with myelomalacia in injured parts of the spinal cord. No severe adverse reactions were observed in any of the patients.

Many experimental studies have been performed to find the optimal period for cell transplantation. To avoid the destruction of transplanted cells by the inflammatory process in the acute phase (<1 week), many researchers consider the subacute phase from 10–14 days as an optimal period for cell transplantation (25). Results from animal studies show that significant gliosis is a major obstacle inhibiting axonal regeneration during the chronic stage. All of our patients accepted MSC therapy in the chronic stage. There was no significant difference in the time from injury to MSC treatment between patients whose clinical symptoms were improved and patients whose symptoms were not improved. These results indicate that the optimal period of MSC transplantation in patients with SCI should not be restricted to <2 weeks after injury.

In conclusion, this study demonstrated that the procedure of intrathecal injection of UC-MSCs was safe, and treatment improved the clinical symptoms of patients with incomplete SCI. However, the improvement was limited in patients with complete SCI and patients with myelomalacia in injured parts of the spinal cord. Further placebo-controlled randomized trials are warranted to study the most suitable times of treatment, the quantity of MSCs and the best procedure for MSC injection.

Disclosure of interest: The authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

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