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Allogeneic umbilical cord blood mononuclear cell therapy for spinal cord injury – a retrospective cohort study

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Abstract

Objective: **Previous studies have reported that human umbilical cord blood-derived stem cell therapy is safe and effective for subjects with Spinal Cord Injury (SCI). The objective of this retrospective cohort study was to analyze the muscle, nerve, urinary, and gastrointestinal function in subjects with SCI, treated with either human umbilical cord blood-derived mononuclear cells (hUCMNCs) or conventional therapy.**

Patients and Methods: **Thirty subjects with SCI were randomly selected from seventy treated with hUCMNCs therapy in the Wuhan Hongqiao Brain Hospital Co., Ltd. (Wuhan, Hubei) between March 2009 and March 2012. Another thirty subjects with SCI, who received only conventional therapy and no hUCMNCs therapy, were included as the control group.**

Results: **Uncultured hUCMNCs were used for therapy of subjects with SCI. No subjects developed adverse reactions, further demonstrating the safety of hUCMNCs therapy. A significantly higher proportion of subjects in the hUCMNCs therapy group showed improved function in pain and temperature sensation, lower limb muscle strength, bladder function, and gastrointestinal function compared to a conventional therapy group.**

Conclusions: **Application of hUCMNCs was effective in the therapy of subjects with SCI. In order to further analyze the safety and efficacy of hUCMNCs therapy for SCI subjects, further prospective studies are warranted.**

INTRODUCTION

Spinal cord injury (SCI) is a common type of severe trauma often resulting in a permanent neurologic deficit. Within the United States, the annual rate of SCI is 10-40 people per million population[1]. SCI is characterized by the demyelination of intact axons and loss of neurons. Neuronal damage leads to sudden loss of sensory, motor, and autonomic function distal to the level of trauma[2-5]. There has been no curative treatment for the neurological deficits of SCI. Current treatment techniques of surgical decompression and fixation with the use of injected anti-inflammatory medications, neurotropic drugs, and physical rehabilitation have failed to achieve satisfactory therapeutic results[6-7]. One of the potential treatment alternatives is stem cell therapy.

Bone marrow-derived cells have been shown to have considerable therapeutic potential for SCI[8-20].

In vitro studies have shown that umbilical cord blood cells secrete a number of cytokines that could be beneficial to recovery following SCI[21-23]. Human umbilical cord blood-derived mononuclear cells (hUCMNCs) include a heterogeneous population of hematopoietic and mesenchymal stem cells, endothelial progenitor cells and immature immunological

cells[24,25]. Several studies have demonstrated that mesenchymal stem cells (MSCs) from various sources hold promise to enhance functional recovery after SCI[26]. Intrathecal, intravenous and intra-spinal administrations have been used for cell transplantation after SCI[27]. Previous studies have reported that human umbilical cord blood stem cell (hUCBSC) therapy is safe and effective and can improve neurological function and quality of life in subjects with SCI[28-31].

Although stem cell therapy after SCI has shown promising results, only a limited number of studies have been conducted thus far. Further research is required for better characterization of the efficacy of stem cell therapy for SCI.

The current retrospective cohort study is aimed to analyze the muscle, nerve, urinary, and gastrointestinal function in SCI subjects treated with either hUCMNCs or conventional therapy.

Patients and methods

Thirty subjects with SCI were randomly selected from seventy treated with hUCMNCs therapy in the Wuhan Hongqiao Brain Hospital Co., Ltd. (Wuhan, Hubei) between March 2009 and March 2012. Another thirty subjects with SCI, who received only conventional therapy and no hUCMNCs therapy, were included as the control group. Baseline characteristics of subjects are presented in Table I.

Purification of hUCMNCs from other elements in the blood sample was conducted by Ficoll-Hypaque density gradient centrifugation. As a result, cells were distributed in the solution in layers based on the differences in their density/size. Collection of human umbilical cord blood from primiparous pregnant women receiving Caesarean section, isolation of mononuclear cells containing MSCs from human umbilical cord blood and the quality control testing were performed according to methods described by Mehling et al (Hackensack, NJ, USA)[32].

This study was approved by an Institutional Review Board of the Wright State University (Office of Research and Sponsored Programs. SC# 5488, "Spinal Cord Injury Stem Cell Therapy").

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). This article does not contain any studies with animal subjects.

Stem cell therapy

Subjects received three injections of 5 ml hUCMNCs (3×10^8) isolated from human umbilical cord blood of three different donors. hUCMNCs were administered intravenously and via lumbar

Table 1. Baseline characteristics of subjects. There were no differences between groups of stem cell and conventional therapy with respect to subjects' age at injury, age at baseline measures, or SCI location.

Patient characteristics	Stem cell therapy (n = 30)	Conventional therapy (n = 30)	*p*-value
Gender (No., %)			
Male	16 (53.3)	27 (90.0)	0.002
Female	14 (46.7)	3 (10.0)	
Spinal cord level of injury (No., %)			
Cervical (C5)	1 (3.3)	2 (6.7)	0.458
Thoracic (T2-T10)	10 (33.3)	14 (46.7)	
Lumbar (L1-L5)	19 (63.3)	14 (46.7)	
Age (yrs) at injury			
Mean	34.2	36.1	0.421
Range	16.6 - 51.8	16.3 - 52.9	
Age (yrs) at baseline measures			
Mean	38.5	41.2	0.237
Range	21.5 - 56.2	24.0 - 55.3	
Time (yrs) from injury to baseline			
Mean	4.3	5.1	0.053
Range	1.5 - 8.4	2.1 - 8.4	

puncture into the cerebrospinal fluid with approximately 1 week between injection numbers 1 and 2, and approximately 2 weeks between injection numbers 2 and 3. Ten of thirty subjects had computed tomography (CT) -guided intramedullary injection at the lesion site. The subjects who underwent CT-guided injections at the level of the lesion were included in the same group as the subjects who underwent stem cell treatment without CT-guided injections for our statistical analysis. The mean (SD) time from baseline to post-treatment measurement was 59 (19) days (range 28-112 days).

Conventional therapy

Subjects received all of the following therapies[33-37]:

- Limb therapy: 1/day x 60, 180, or 220 days;
- Electrotherapy: 1/day x 60 days;
- Low frequency spinal cord stimulation (10 spots): 1/day x 60 or 90 days;
- Electronic biofeedback therapy: 6/day x 44 days, 1/day x 90 days, or 6/day x 120 days;
- Acupuncture: 2/day x 44 days, 120 days, or 130 days.

The mean (SD) time from baseline to post-treatment measurement was 192 (104) days (range 58-550 days).

Outcomes assessed and scales used

- Pain and temperature sensation was graded on a 0/1 point scale (0 = none, 1 = normal).
- Upper and lower limb muscle strength was graded on a five-point scale (0 = total paralysis, 5 = (normal) active movement).
- Bladder function was graded on a three-point scale (0=incontinence, 1=catheterization, 2 = normal).
- Gastrointestinal function was graded on a 0/1 point scale (0=incontinence, 1=normal).

Data analysis

Comparisons between groups were made with two-sample *t*-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.

Results

Pain sensation

Pain sensation testing of thirty stem cell therapy subjects showed that twenty-six scored 0 and four scored 1 at baseline. After therapy, four scored 0 and twenty-six scored 1. Of the thirty conventional therapy subjects, twenty-eight scored 0 and two scored 1 at baseline. After therapy, twenty-six scored 0 and four scored 1 (Figure 1). The difference between the groups of subjects having stem cell and conventional therapy was statistically significant ($p<0.001$).

Temperature sensation

All thirty stem cell and conventional therapy group subjects scored 0 at baseline assessment. After stem cell therapy, nine subjects scored 1. No changes in temperature sensation were observed after the conventional therapy (Figure 2). This resulted in a statistically significant difference between subjects having stem cell and those receiving conventional therapy ($p=0.002$).

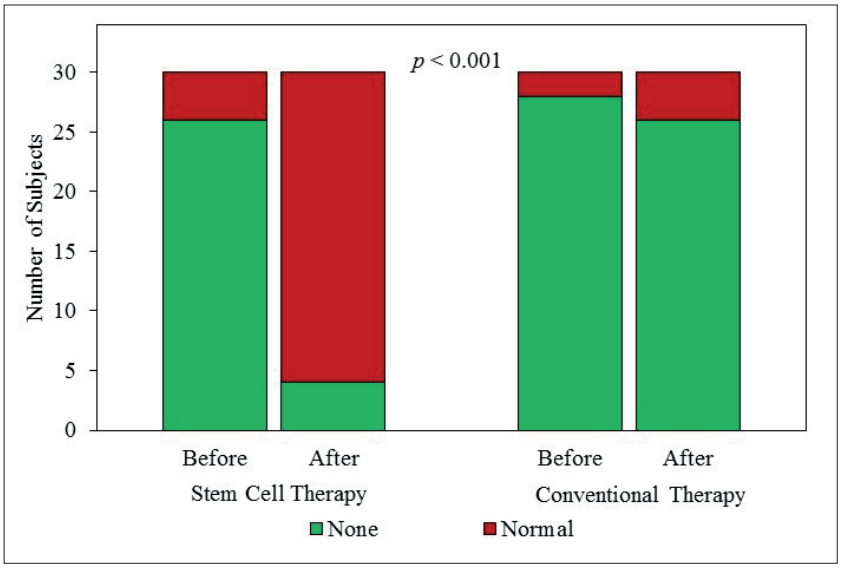

Figure 1. Analysis of pain sensation before and after hUCMNC therapy showed the statistically significant difference between the groups of subjects having stem cell and conventional therapy ($p<0.001$).

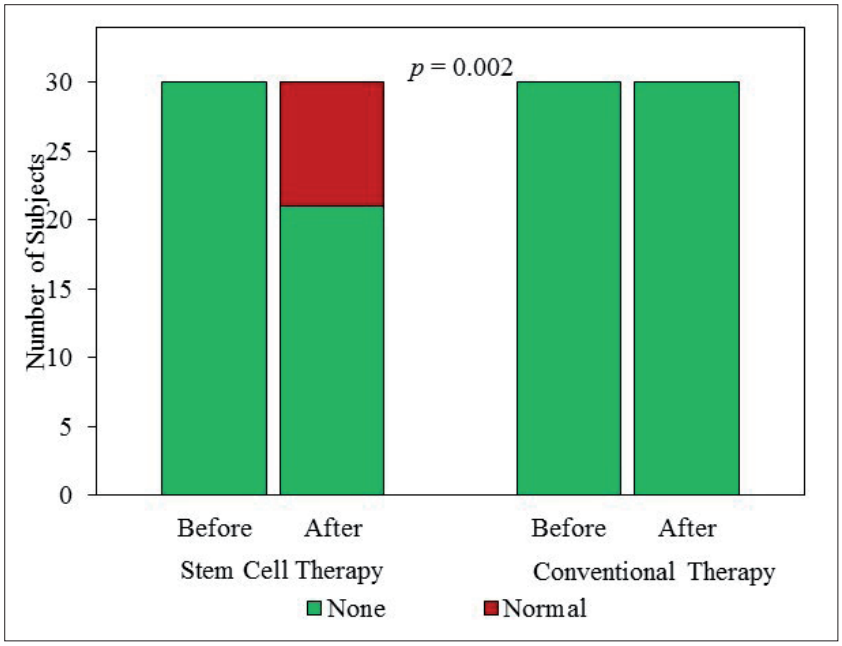

Figure 2. Analysis of temperature sensation before and after hUCMNC therapy showed a statistically significant difference between the groups of subjects having stem cell and conventional therapy (p=0.002).

Upper and lower limb muscle strength

Upper limb muscle strength measurements of thirty stem cell therapy subjects showed that two subjects scored 1, seven subjects scored 2, two subjects scored 3 and nineteen subjects scored 5 at baseline assessment. After therapy, one subject scored 2, six subjects scored 4 and twenty-three subjects scored 5.

In the conventional therapy group, four subjects scored 2, two subjects scored 3, four subjects scored 4 and nineteen subjects scored 5 at baseline assessment. After therapy, three subjects scored 2, one patient scored 3, six subjects scored 4 and nineteen subjects scored 5 (Figure 3).

There is a statistically significant difference between groups of subjects having a stem cell versus conventional therapy (p = 0.005).

Lower limb muscle strength measurements of thirty stem cell therapy subjects showed that twenty-five subjects scored 0, three subjects scored 3 and two subjects scored 2 at baseline assessment. After therapy, seven subjects scored 0, eleven subjects scored 1 and twelve subjects scored 2.

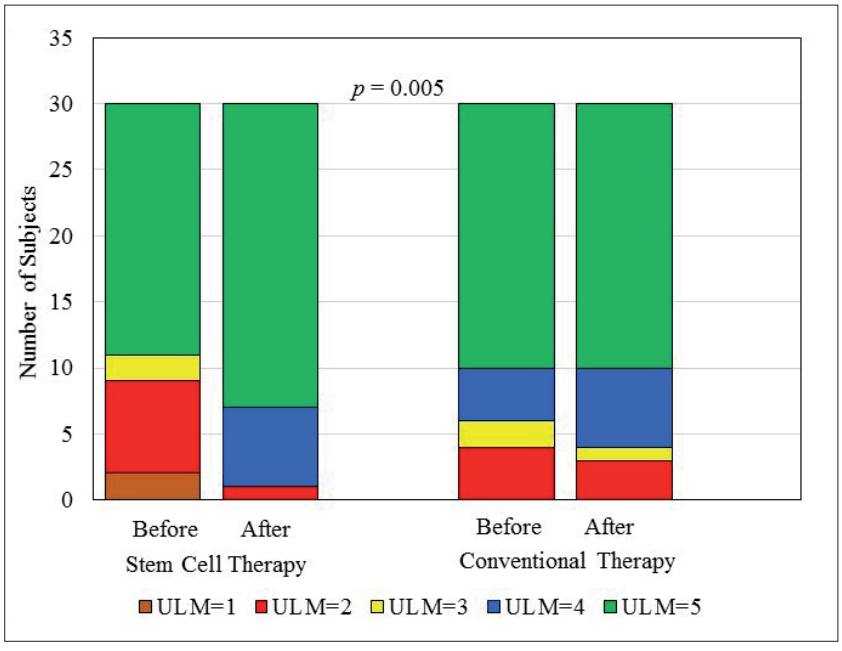

Figure 3. Analysis of upper limb muscle (ULM) strength before and after hUCMNC therapy showed a statistically significant difference between the groups of subjects having stem cell and conventional therapy (p=0.005).

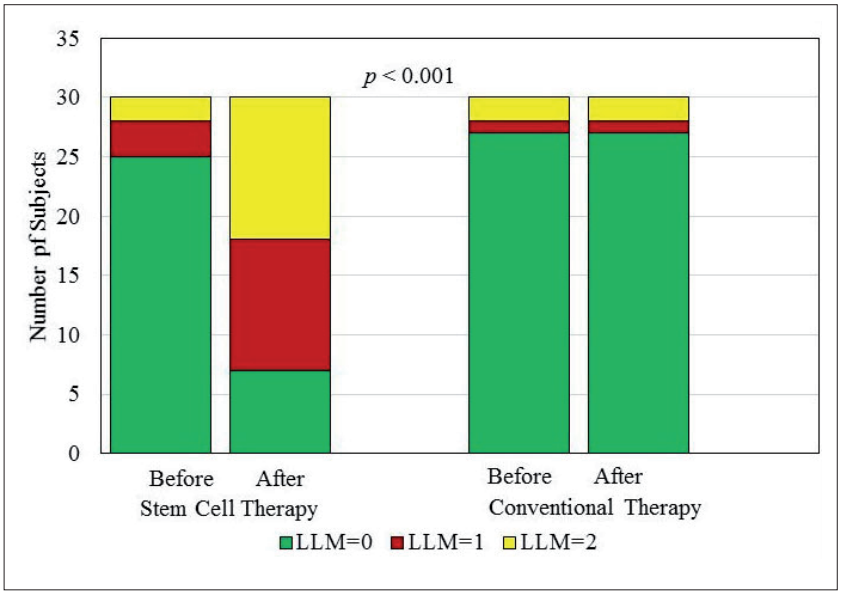

Figure 4. Analysis of lower limb muscle (LLM) strength before and after hUCMNC therapy showed a statistically significant difference between the groups of subjects having stem cell and conventional therapy (p<0.001).

Twenty-seven out of thirty conventional therapy subjects scored 0, one scored 1 and two subjects scored 2. After therapy, the patient scores remained unchanged (Figure 4).

There is a statistically significant difference between groups of subjects having stem cell versus conventional therapy ($p < 0.001$).

Bladder function

All thirty stem cell and conventional therapy group subjects scored 0 at baseline assessment. After stem cell therapy, three subjects scored 0, twenty-five subjects scored 1 and two subjects scored 2.

Twenty-six out of thirty conventional therapy subjects scored 0 and four scored 1. After therapy, the patient scores remained unchanged (Figure 5). There is a statistically significant difference between subjects having stem cell versus conventional therapy ($p < 0.001$).

Gastrointestinal function

All thirty stem cell therapy subjects scored 0 at baseline measurements. After therapy, twenty-seven subjects scored 1.

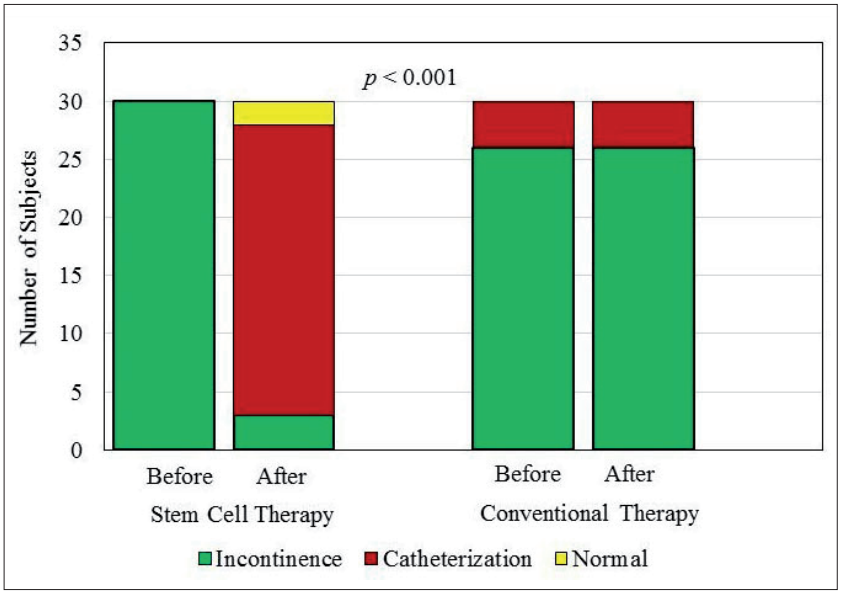

Figure 5. Analysis of bladder function before and after hUCMNC therapy showed a statistically significant difference between the groups of subjects having stem cell and conventional therapy (p<0.001).

Twenty-six out of twenty-seven conventional therapy subjects scored 0 and one scored 1 at baseline measurements with no changes after therapy. The difference between groups was statistically significant ($p < 0.001$).

Discussion

SCI is a potentially disabling condition that is associated with a variety of functional deficits[38].

hUCBSC therapy after SCI has shown promising results, but only a limited number of animal studies and clinical trials have been conducted thus far.

In the current retrospective cohort study, we analyzed the effect of hUCMNCs therapy on recovery of muscle, nerve, urinary, and gastrointestinal function in subjects with SCI. Our study demonstrates that sensory and motor function in the majority of subjects with SCI may improve significantly following stem cell therapy.

Pain and abnormal regulation of body temperature are frequent conditions associated with SCI. Two-thirds of subjects with SCI suffer from some form of pain and one-third suffer from severe pain[39]. Significant reduction of neuropathic pain was observed after combined injection of allogeneic MSCs and expanded umbilical cord blood CD34 cells in subjects with incomplete SCI[30,40]. Shroff et al[41] demonstrated improvement in the sensation of temperature, touch, and pain after stem cell therapy. Disability after SCI is characterized by muscle denervation or disuse atrophy as well as severe urologic dysfunction[42-44]. In the study by Cheng et al[31], administration of umbilical cord blood mesenchymal stem cells showed improvement of motor ability, muscle tension, self-care ability and urologic function in subjects with SCI. In addition to the immediate loss of sensation and motor function, 11% of hospitalizations in subjects with SCI are connected to gastrointestinal complications[45]. A clinical trial of twenty subjects with SCI conducted by Jiang et al[20] demonstrated significant improvement in muscle, urinary and gastrointestinal function after autologous human bone marrow-derived mesenchymal stem cell therapy.

In above-mentioned studies, human embryonic stem cells, expanded umbilical cord blood CD34 cells, expanded Wharton's jelly MSCs and bone marrow-derived mesenchymal stem cell have been used. The stem cell expansion process is lengthy, and there is a risk of contamination and altered cellular properties.

Conclusions

In summary, fresh uncultured hUCMNCs were used for therapy of subjects with SCI. No subjects developed adverse reactions, further demonstrating the safety of hUCMNCs therapy. A significantly higher proportion of subjects in the hUCMNCs therapy group showed improved function in pain and temperature sensation, lower limb muscle strength, bladder function and gastrointestinal function compared to the conventional therapy group.

Due to the limited number of subjects and the retrospective nature of the study, we were not able to relate the efficacy of hUCMNCs therapy to modality, administration route, and variables such as age, gender, time and cause of the injury. In order to further analyze the safety and efficacy of hUCMNCs therapy for SCI subjects, further prospective studies are warranted.

Declaration of Funding Interests:
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Authors' declaration of personal interests:
BM, D-CW, LQ, SR: critical revision of the manuscript; AP: project oversight; AS: statistical analysis; BS: data preparation and analysis; MM, RR: drafting the manuscript.

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