

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

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Keywords: Spinal cord injury (SCI), Human umbilical cord blood-derived mononuclear cells (hUCMNCs), Mesenchymal stem cells (MSCs), Human umbilical cord blood stem cells (hUCBSCs).

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 population¹. 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 trauma²⁻⁵. 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 results⁶⁻⁷. One of the potential treatment alternatives is stem cell therapy.

Bone marrow-derived cells have been shown to have considerable therapeutic potential for SCI⁸⁻²⁰.

In vitro studies have shown that umbilical cord blood cells secrete a number of cytokines that could be beneficial to recovery following SCI²¹⁻²³. 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 SCI²⁶. Intrathecal, intravenous and intra-spinal administrations have been used for cell transplantation after SCI²⁷. 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 SCI²⁸⁻³¹.

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 therapies³³⁻³⁷:

- 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 ($p = 0.002$).

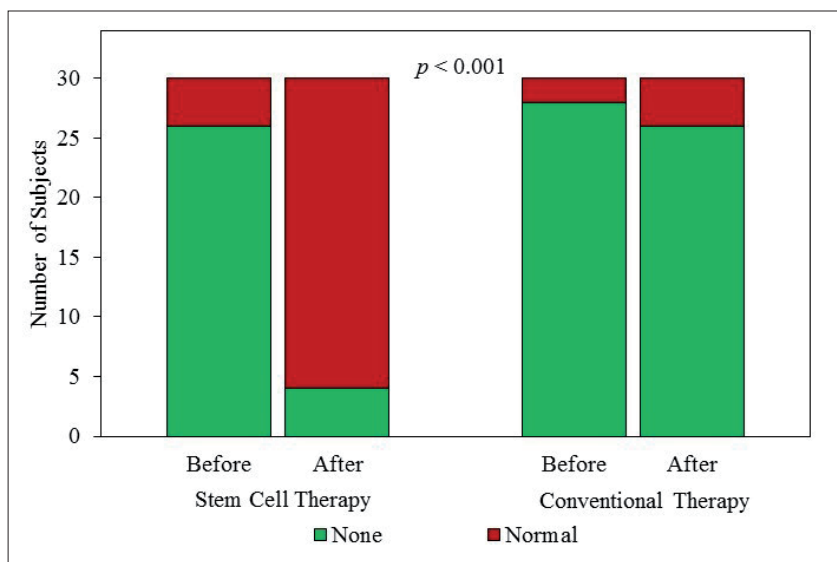


Figure 1. Analysis of pain sensation before and after hUCMNC therapy showed the statistically significant difference between the groups of subjects having stem cell and conventional therapy ($p < 0.001$).

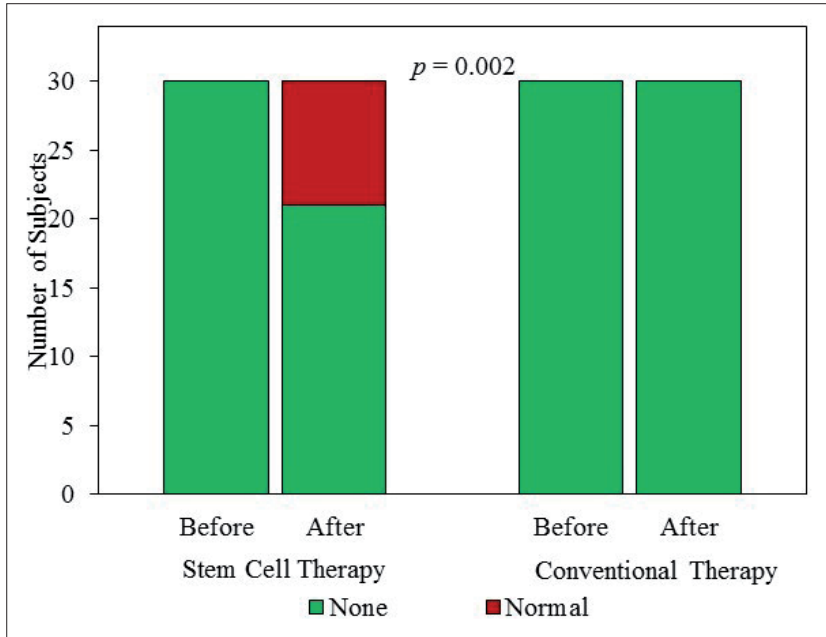


Figure 2. Analysis of temperature sensation before and after hUCMNC therapy showed a statistically significant difference between the groups of subjects having stem cell and conventional therapy ($p=0.002$).

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.

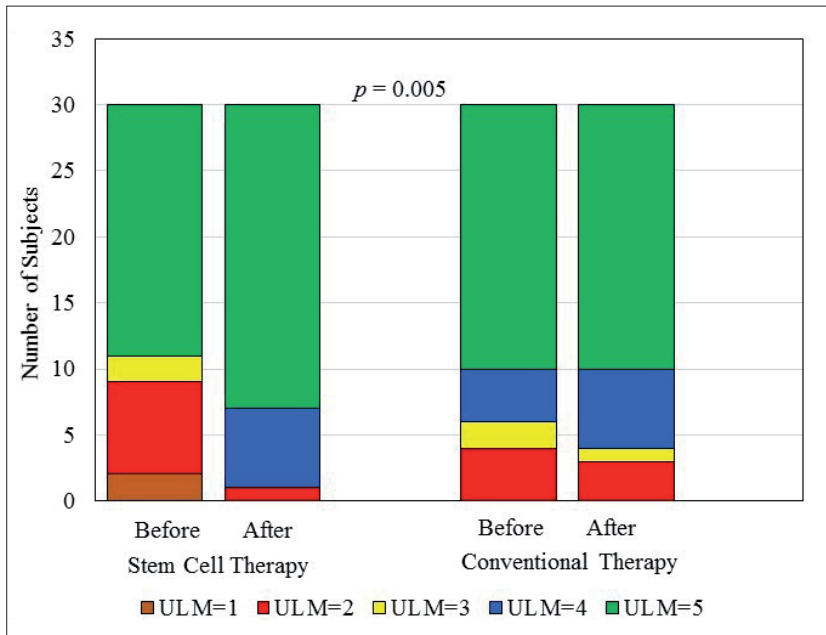
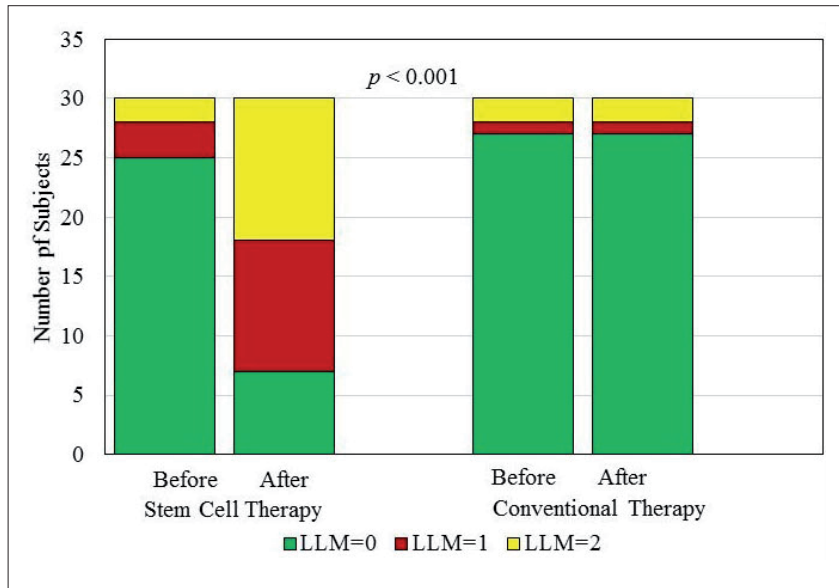


Figure 3. Analysis of upper limb muscle (ULM) strength before and after hUCMNC therapy showed a statistically significant difference between the groups of subjects having stem cell and conventional therapy ($p=0.005$).

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.

ty-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.

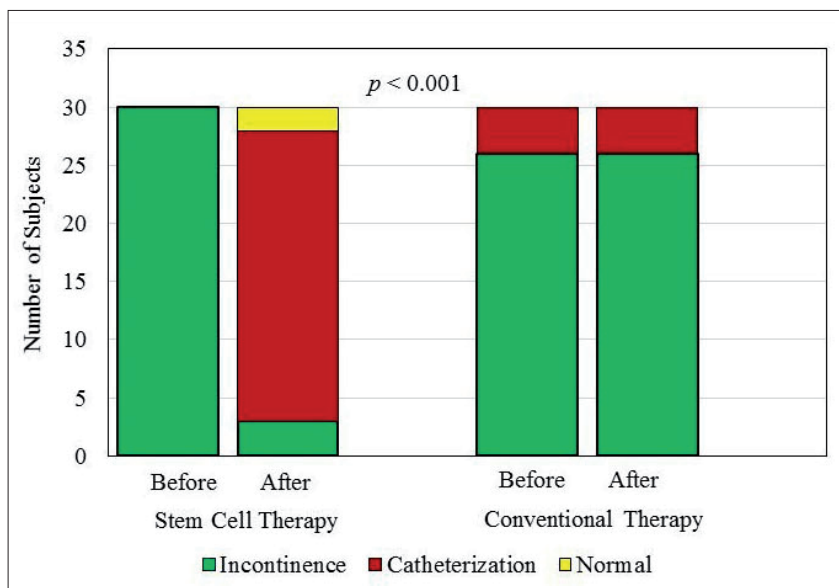


Figure 5. Analysis of bladder function before and after hUCMNC therapy showed a statistically significant difference between the groups of subjects having stem cell and conventional therapy ($p < 0.001$).

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 deficits³⁸.

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 pain³⁹. 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 al⁴¹ 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 dysfunction⁴²⁻⁴⁴. In the study by Cheng et al³¹, 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 complications⁴⁵. A clinical trial of twenty subjects with SCI conducted by Jiang et al²⁰ 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:

This study was sponsored by BHI Therapeutic Sciences. Fees for the study were subsidized by Blue Horizon Charitable Foundation. Brian Mehling is the president and Chief Medical Officer at BHI Therapeutic Sciences.

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.

REFERENCES

1. Cadotte DW, Fehlings MG. Spinal cord injury: a systematic review of current treatment options. *Clin Orthop Relat Res* 2011; 469: 732-741.
2. Anderberg L, Aldskogius H, Holtz A. Spinal cord injury-scientific challenges for the unknown future. *Med Sci* 2007; 112: 259-288.
3. Thuret S, Moon LD, Gage FH. Therapeutic interventions after spinal cord injury. *Nat Rev Neurosci* 2006; 7: 628-643.
4. Bradbury EJ, Moon LD, Popat RJ, King VR, Bennett GS, Patel PN, Fawcett JW, McMahon SB. Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature* 2002; 416: 636-640.
5. Ogawa Y, Sawamoto K, Miyata T, Miyao S, Watanabe M, Nakamura M, Bregman BS, Koike M, Uchiyama Y, Toyama Y, Okano H. Transplantation of in vitro-expanded fetal neural progenitor cells results in neurogenesis and functional recovery after spinal cord contusion injury in adult rats. *J Neurosci Res* 2002; 69: 925-933.
6. Mothe AJ, Tator CH. Advances in stem cell therapy for spinal cord injury. *J Clin Invest* 2012; 122: 3824-3834.
7. Tator CH. Review of treatment trials in human spinal cord injury: issues, difficulties, and recommendations. *Neurosurgery* 2006; 59: 957-982.

8. Park HC, Shim YS, Ha Y, Yoon SH, Park SR, Choi BH, Park HS. Treatment of complete spinal cord injury patients by autologous bone marrow cell transplantation and administration of granulocyte-macrophage colony stimulating factor. *Tissue Eng* 2005; 11: 913-922.
9. Callera F, do Nascimento RX. Delivery of autologous bone marrow precursor cells into the spinal cord via lumbar puncture technique in patients with spinal cord injury: a preliminary safety study. *Exp Hematol* 2006; 34: 130-131.
10. Chernykh ER, Stupak VV, Muradov GM, Sizikov MY, Shevela EY, Leplina OY, Tikhonova MA, Kulagin AD, Lisukov IA, Ostanin AA, Kozlov VA. Application of autologous bone marrow stem cells in the therapy of spinal cord injury patients. *Bull Exp Biol Med* 2007; 143: 543-547.
11. Yoon SH, Shim YS, Park YH, Chung JK, Nam JH, Kim MO, Park HC, Park SR, Min BH, Kim EY, Choi BH, Park H, Ha Y. Complete spinal cord injury treatment using autologous bone marrow cell transplantation and bone marrow stimulation with granulocyte macrophage-colony stimulating factor: phase I/II clinical trial. *Stem Cells* 2007; 25: 2066-2073.
12. Deda H, Inci MC, Kürekçi AE, Kayihan K, Özgün E, Ustünsoy GE, Kocabay S. Treatment of chronic spinal cord injured patients with autologous bone marrow-derived hematopoietic stem cell transplantation: 1-year follow-up. *Cytotherapy* 2008; 10: 565-574.
13. Saito F, Nakatani T, Iwase M, Maeda Y, Hirakawa A, Murao Y, Suzuki Y, Onodera R, Fukushima M, Ide C. Spinal cord injury treatment with intrathecal autologous bone marrow stromal cell transplantation: the first clinical trial case report. *J Trauma* 2008; 64: 53-59.
14. Geffner LF, Santacruz P, Izurieta M, Flor L, Maldonado B, Auad AH, Montenegro X, Gonzalez R, Silva F. Administration of autologous bone marrow stem cells into spinal cord injury patients via multiple routes is safe and improves their quality of life: comprehensive case studies. *Cell Transplant* 2008; 17: 1277-1293.
15. Kumar AA, Kumar SR, Narayanan R, Arul K, Baskaran M. Autologous bone marrow-derived mononuclear cell therapy for spinal cord injury: a phase I/II clinical safety and primary efficacy data. *Exp Clin Transplant* 2009; 7: 241-248.
16. Pal R, Venkataramana NK, Bansal A, Balaraju S, Jan M, Chandra R, Dixit A, Rauthan A, Murgod U, Totey S. Ex vivo-expanded autologous bone marrow-derived mesenchymal stromal cells in human spinal cord injury/paraplegia: a pilot clinical study. *Cytotherapy* 2009; 11: 897-911.
17. Moviglia GA, Fernandez Viña R, Brizuela JA, Saslavsky J, Vrsalovic F, Varela G, Bastos F, Farina P, Etchegaray G, Barbieri M, Martinez G, Picasso F, Schmidt Y, Brizuela P, Gaeta CA, Costanzo H, Moviglia Brandolino MT, Merino S, Pes ME, Veloso MJ, Rugilo C, Tamer I, Shuster GS. Combined protocol of cell therapy for chronic spinal cord injury. Report on the electrical and functional recovery of two patients. *Cytotherapy* 2006; 8: 202-209.
18. Attar A, Ayten M, Ozdemir M, Ozgencil E, Bozkurt M, Kaptanoglu E, Beksac M, Kanpolat Y. An attempt to treat patients who have injured spinal cords with intrathecal implantation of concentrated autologous bone marrow cells. *Cytotherapy* 2011; 13: 54-60.
19. Kishk NA, Gabr H, Hamdy S, Afifi L, Abokresha N, Mahmoud H, Wafaie A, Bilal D. Case control series of intrathecal autologous bone marrow mesenchymal stem cell therapy for chronic spinal cord injury. *Neurorehabil Neural Repair* 2010; 24: 702-708.
20. Jiang PC, Xiong WP, Wang G, Chao M, Yao WQ, Kendall SF, Mehling BM, Yuan XH, Wu DC. A clinical trial report of autologous bone marrow derived mesenchymal stem cell transplantation in subjects with spinal cord injury. *Exp Ther Med* 2013; 6: 140-146.
21. Liu CH, Hwang SM. Cytokine interactions in mesenchymal stem cells from cord blood. *Cytokine* 2005; 32: 270-279.
22. Newman MB, Willing AE, Manresa JJ, Sanberg CD, Sanberg PR. Cytokines produced by cultured human umbilical cord blood (HUCB) cells: implications for brain repair. *Exp Neurol* 2006; 199: 201-208.
23. Neuhoff S, Moers J, Rieks M, Grunwald T, Jensen A, Dermietzel R, Meier C. Proliferation, differentiation, and cytokine secretion of human umbilical cord blood-derived mononuclear cells in vitro. *Exp Hematol* 2007; 35: 1119-1131.
24. Yang WZ, Zhang Y, Wu F, Min WP, Minev B, Zhang M, Luo XL, Ramos F, Ichim TE, Riordan NH, Hu X. Safety evaluation of allogeneic umbilical cord blood mononuclear cell therapy for degenerative conditions. *J Transl Med* 2010; 8: 75.
25. Javed MJ, Mead LE, Prater D, Bessler WK, Foster D, Case J, Goebel WS, Yoder MC, Haneline LS, Ingram DA. Endothelial colony forming cells and mesenchymal stem cells are enriched at different gestational ages in human umbilical cord blood. *Pediatr Res* 2008; 64: 68-73.
26. Dasari VR, Veeravalli KK, Dinh DH. Mesenchymal stem cells in the treatment of spinal cord injuries: a review. *World J Stem Cells* 2014; 6: 120-133.
27. Quertainmont R, Cantinieaux D, Botman O, Sid S, Schoenen J, Franzen R. Mesenchymal stem cell graft improves recovery after spinal cord injury in adult rats through neurotrophic and pro-angiogenic actions. *PLoS One* 2012; 7: e39500.
28. Yao L, He C, Zhao Y, Wang J, Tang M, Li J, Wu Y, Ao L, Hu X. Human umbilical cord blood stem cell transplantation for the treatment of chronic spinal cord injury: Electrophysiological changes and long-term efficacy. *Neural Reg Res* 2013; 8: 397-403.
29. Liu J, Han D, Wang Z, Xue M, Zhu L, Yan H, Zheng X, Guo Z, Wang H. Clinical analysis of the treatment of spinal cord injury with umbilical cord mesenchymal stem cells. *Cytotherapy* 2013; 15: 185-191.
30. Ichim TE, Solano F, Lara F, Paris E, Ugalde F, Rodriguez JP, Minev B, Bogin V, Ramos F, Woods EJ, Murphy MP, Patel AN, Harman RJ, Riordan NH. Feasibility of combination allogeneic stem cell therapy for spinal cord injury: a case report. *International archives of medicine* 2010; 3: 30. *Int Arch Med* 2010; 3: 30.
31. Cheng H, Liu X, Hua R, Dai G, Wang X, Gao J, An Y. Clinical observation of umbilical cord mesenchymal stem cell transplantation in treatment for sequelae of thoracolumbar spinal cord injury. *J Transl Med* 2014; 12: 253.

32. Mehling BM, Quartararo L, Manvelyan M, Wang P, Wu DC. Evaluation of immune response to intravenously administered human cord blood stem cells in the treatment of symptoms related to chronic inflammation. *J Stem Cell Res Ther* 2015; 5: 8.
33. Janice J Eng, Pei Fang Tang. Gait training strategies to optimize walking ability in people with stroke: a synthesis of the evidence. *Expert Rev Neurother* 2007; 7: 1417-1436.
34. Tan G, Rintala DH, Thornby JI, Yang J, Wade W, Vasilev C. Using cranial electrotherapy stimulation to treat pain associated with spinal cord injury. *J Rehabil Res Dev* 2006; 43: 461-474.
35. Jeon YH. Spinal cord stimulation in pain management: a review. *Korean J Pain* 2012; 25: 143-150.
36. Middaugh S, Thomas KJ, Smith AR, McFall TL, Klingmueller J. EMG biofeedback and exercise for treatment of cervical and shoulder pain in individuals with a spinal cord injury: a pilot study. *Top Spinal Cord Inj Rehabil* 2013; 19: 311-323.
37. Heo I, Shin BC, Kim YD, Hwang EH, Han CW, Heo KH. Acupuncture for spinal cord injury and its complications: a systematic review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med* 2013; 2013: 364216
38. Iseli E, Cavigelli A, Dietz V, Curt A. Prognosis and recovery in ischemic and traumatic spinal cord injury: clinical and electrophysiological evaluation. *J Neurol Neurosurg Psychiatry* 1999; 67: 567-571.
39. Teasell RW, Mehta S, Aubut JA, Foulon B, Wolfe DL, Hsieh JT, Townson AF, Short C; Spinal Cord Injury Rehabilitation Evidence Research Team. A systematic review of pharmacological treatments of pain following spinal cord injury. *Arch Phys Med Rehabil* 2010; 91: 816-831.
40. Leung L. Cellular therapies for treating pain associated with spinal cord injury. *J Transl Med* 2012; 10: 37.
41. Shroff G, Gupta R. Human embryonic stem cells in the treatment of subjects with spinal cord injury. *Ann Neurosci* 2015; 22: 208-216.
42. Jayaraman A, Shah P, Gregory C, Bowden M, Stevens J, Bishop M, Walter G, Behrman A, Vandeborne K. Locomotor training and muscle function after incomplete spinal cord injury: case series. *J Spinal Cord Med* 2008; 31: 185-193.
43. Gordon T, Mao J. Muscle atrophy and procedures for training after spinal cord injury. *Phys Ther* 1994; 74: 50-60.
44. Weiss DJ, Fried GW, Chancellor MB, Herbison GJ, Ditunno JF Jr, Staas WE Jr. Spinal cord injury and bladder recovery. *Arch Phys Med Rehabil* 1996; 77: 1133-1135.
45. Holmes GM. Upper gastrointestinal dysmotility after spinal cord injury: is diminished vagal sensory processing one culprit? *Front Physiol* 2012; 3: 277.