

Review Article

The Applications of Human Umbilical Cord Mesenchymal Stem Cells to Treat Spinal Cord Injuries

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Abstract

Due to the morbidity and resulting lifestyle changes of Spinal Cord Injuries (SCI), there has been an extensive need to evaluate potential treatments. Mesenchymal cells hold the capacity to address both the primary and secondary mechanisms of SCI. Human Umbilical Cord stem cells (hUC), in particular, show promise due to their rapid proliferation, immunological properties, and pluripotent capacity. These hUC-MSCs can be isolated from the umbilical Cord Blood (hCB) and Wharton's jelly, a viscous gel that maintains the umbilical cord's integrity. While Wharton's jelly-derived hUC-MSCs appear to have a greater capability for the treatment of SCI due to their increased proliferation, hCB-MSCs additionally has long-term therapeutic potential in clinical trials.

Keywords: Spinal Cord Injuries; Mesenchymal Stem Cells; Amyotrophic Lateral Sclerosis; Visual Analogue Scale

Abbreviations

ALS: Amyotrophic Lateral Sclerosis; ASAI: American Spinal Injury Association; AT-MSCs: Adipose Tissue Mesenchymal Stem Cells; BFGF: Basic Fibroblast Growth Factor; BM-MSCs: Human Bone Marrow Mesenchymal Stem Cells; ECM: Extracellular Matrix; GDNF: Glial-Derived Neurotrophic Factor; HPB- MSC: Human Peripheral Blood Mesenchymal Stem Cells; HSC: Haematopoietic Stem Cells; Hes: Human Embryonic Stem Cell; HUC-MSCs: Human Umbilical Cord Blood Mesenchymal Stem Cells; HWJ-MSCs: Human Wharton's Jelly Mesenchymal Stem Cells; MCS: Mental Component Summary; MSC: Mesenchymal Stem Cells; NGF: Nerve Growth Factor; ODI: Oswestry Disability Scale; OVCF: Osteoporotic Vertebral

Compression Fracture; PCS: Physical Component Summary; SCI: Spinal Cord Injury; SF: Short Form; VAS: Visual Analogue Scale

Introduction

The impact of Spinal Cord Injuries (SCI) is influenced by both socioeconomic factors and injury etiology. For more developed countries, SCI typically involves personal and/or physical restrictions that can often be alleviated. Technological advances and prevention methods effectively reduce the mortality of these neurological injuries. Undeveloped countries, however, face higher terminal conditions regarding SCI. This can be due to a lack of medical resources, a deficiency of rehabilitation services, or established social expectations [1].

SCI classification additionally determines the injury outcome. SCI can be both traumatic and nontraumatic. A traumatic SCI can further be divided into primary and secondary mechanisms. During a primary acute SCI, the initial injury is the result of energy transfer and localized distortion. Examples of primary mechanisms include blunt force trauma, lacerations, and over-flexion.

This is followed by the secondary mechanism of proceeding biochemical and cellular damage. Secondary mechanisms include both local and systemic changes, ranging from vascular damage to decreased cardiac output. The combination of both primary and secondary mechanisms during a traumatic SCI requires multifaceted rehabilitation [2]. Nontraumatic SCI, which is increasingly prevalent due to the aging American population, is more common than traumatic SCI [3]. The top three causes of nontraumatic SCI include tumors (20.1%), multiple sclerosis (19.4%), and degeneration that is unrelated to trauma (17.9%). Between both traumatic and nontraumatic SCI, a noticeable age trend can be viewed between the diagnoses. The younger population tends to be commonly admitted due to traumatic SCI, while the geriatric population experiences a higher quantity of nontraumatic SCI [4].

Treatments for SCI are determined by the American Spinal Injury Association (ASAI) scale. This scale takes account of motor and sensory deficits to determine if the injury is complete or incomplete [5]. The ASIA impairment scale is seen in Table 1.

A	Complete	No motor or sensory function is preserved in the sacral segments S4-S5.
B	Incomplete	Sensory function is preserved, but motor function is not preserved below the neurological level and including the sacral segments S4-S5.
C	Incomplete	Motor function is preserved below the neurological level, and more than half of the key muscles below the neurological level have a muscle grade less than 3.
D	Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
E	Normal	Motor and sensory functions are normal.

Table 1: American spinal injury association scale for partial and impartial spinal cord injuries [5].

One particular treatment that holds promise for spinal cord injury rehabilitation is the use of stem cell therapy. Stem cells, known for their emphasis on cellular differentiation and proliferation, are the origins of most adult cell lineages. Their multipotential properties have led to multiple studies regarding their differentiation potential. Mesenchymal Stem Cells (MSC), which originate from mesenchymal tissue, particularly have the pluripotent capability to differentiate into non-mesenchymal cells [6]. Multiple MSC has been identified, including adipose tissue, the perivascular zone, synovial fluid/membrane, fetal liver, urine, endometrial tissue, umbilical cord blood, umbilical cord tissue, and Wharton's Jelly [7]. Ethical issues regarding consent acquisition and the risk of harm continue to direct research toward MSC sources that are easier to obtain [8]. Umbilical cord MSC shows primary consideration for stem cell isolation due to its lack of ethical concerns and general view as medical waste [9]. Perinatal stem cells have been shown to both circumnavigate the limitations of fetal stem cell acquisition, which removes fetal potential for life, and alleviate the adult stem cell limitations of reduced multipotential [10]. This review, therefore, focuses on the potential of umbilical stem cell therapy on spinal cord injuries due to its availability, ethical alleviations, and medical possibilities.

Umbilical Cord Anatomy

The umbilical cord, a tubular structure known for its involvement in gestation, is a complex organ that ensures fetal vitality. The cord itself has three blood vessels surrounded by a gel-like substance called Wharton's Jelly [11]. These vessels, an umbilical vein and two paired umbilical arteries, exchange oxygenated and deoxygenated blood between the placenta and fetus. As the umbilical arteries converge, around 5 cm from the insertion of the cord, the blood pressure and flow are equalized between the placental and umbilical arteries. This artery junction is called Hyrtl's anastomosis. Wharton's Jelly additionally surrounds the remnants of the allantois. The cord itself averages from 50 cm to 60 cm in length, with an approximate 1 cm diameter, and lacks both extrinsic and intrinsic innervation [12,13]. Altogether, the umbilical cord is surrounded by amniotic epithelial cells. These epithelial cells, which are initially stratified squamous near the abdominal wall, transform into stratified columnar cells, columnar cells, and then later cuboidal epithelium cells near the placenta [14]. Fig. 1 shows a histology section of an umbilical cord for vascular structure [15].

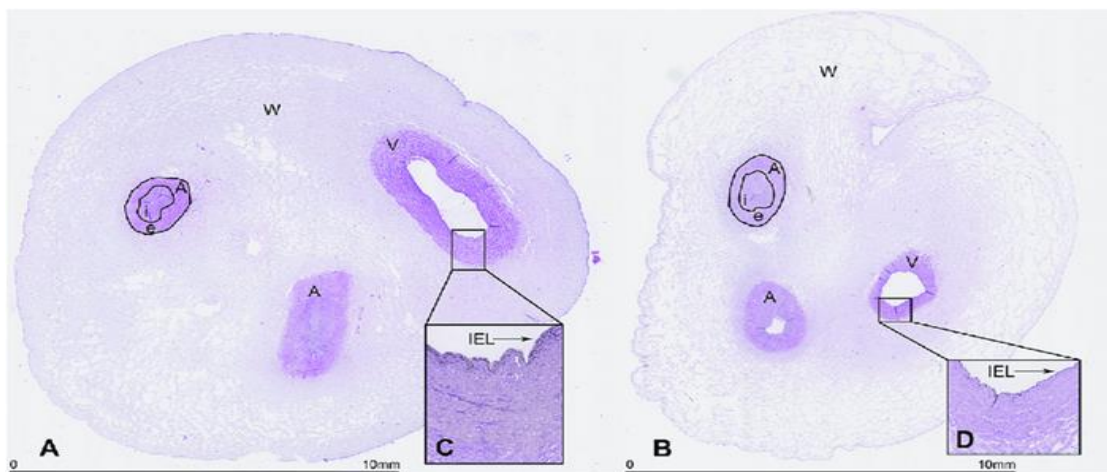


Figure 1: Histology slide of an umbilical cord. The Paraffin section was stained with Haematoxylin Eosin. Arteries (A) consist of a double-layered muscular wall of longitudinal and crossing-spiraled smooth muscle. Veins (V) have a single layer of smooth muscle lined with an Internal Elastic Lamina (IEL). Vessels are surrounded by Wharton's Jelly (WJ) [15].

Wharton's Jelly Stem Cell Therapy

As the gelatinous connective tissue that supports the umbilical vessels, Wharton's Jelly (WJ) plays an important role in the prevention of cord compression and torsion [11]. The marker expression and proliferation efficiency of the perinatal stem cells from WJ are dependent on isolation methods. These methods include enzymatic-derived, explant isolation, or a combination of the two [16]. WJ-MSCs additionally maintain a higher quantity of Human Embryonic Stem Cell (hES) and pluripotent stem cell markers when compared to Bone Marrow (BM) and Adipose Tissue (AT) stem cells during both early and late passages. hES protein markers include NANOG, DNMT3B, and GABRB3. This increased quantity of hES markers indicates that WJ-MSCs have a higher capacity for self-renewal and differentiation [17]. Alongside the higher hES and pluripotent MSC quantity, WJ-MSCs have also been shown to carry a superior capacity for neural differentiation. WJ-derived cells were shown to secrete higher levels of neurotrophic factors such as bFGF -a basic fibroblast growth factor-, NGF -a nerve growth factor-, NT3, NT4, and GDNF -a glial cell line-derived neurotrophic factor- when compared to BM-MSC and AT-MSC [18].

It is further indicated that WJ-MSC has low immunogenicity responses and non-tumorigenic properties. A study conducted by Zhou and colleagues showed a lack of hematopoietic lineage markers, such as CD34 and MHC-II, and a decreased expression of MHC-I. The lack of these markers, which are closely related to graft vs host infections, points to the potential WJ-MSC reduction in immunological response [19]. WJ-MSC was also shown to not induce tumor proliferation or affect the apoptotic potential of lung cancer cells. Due to its properties to not induce drug resistance in cancer cells, it was determined that the WJ-MSC secretome is safe for medical purposes such as neurogenesis [20]. Animal models have played a significant role in WJ stem cell therapy for SCI. A study conducted by Krupa and colleagues evaluated the effects of human Wharton Jelly's MSC (hWJ-MSC) dosage for the ischemic-compression model of SCI in rats [21]. Previous studies have shown an improvement in motor function recovery and regulation of gila scar formation in rats after intrathecal implantation of MSCs for SCI [22,23]. The study on the ischemic-compression model of SCI in rats, however, is significant due to its evaluation of hWJ-MSC and its dosage (Fig. 2). After hWJ-MSC intrathecal implantation in Wistar rats with spinal cord compression lesions, which was 7 days after lesion induction, hind limb motor function, and histology were analyzed. Intrathecal implantation was chosen due to its reduced need for deep anesthesia and wide disbursement of cells around the lesion site and subarachnoid space. Hind limb motor functions as assessed via a BBB test, rotarod test, beam walk test, and time score per hWJ-MSC dosage over time. Histology was measured by comparing white and gray matter sparing and quantifying axon sprouting per hWJ-MSC dosage over time. The mice were injected with either the saline solution control, 0.5 M MSC, 1.5 M MSC, 3 x 0.5 M MSC, or 3 x 1.5 M MSC. It was determined that the rats treated with 1.5 M MSC, 3 x 0.5 M MSC, or 3 x 1.5 M MSC had comparable results and showed significant differences when compared to the control group and the 0.5 M MSC treatment. The control group and the 0.5 M MSC treatment had no significant difference indicated. Gray matter preservation additionally showed a significant difference between the 3 x 1.5 M MSC and the control, however, white matter preservation significance was not found [21].

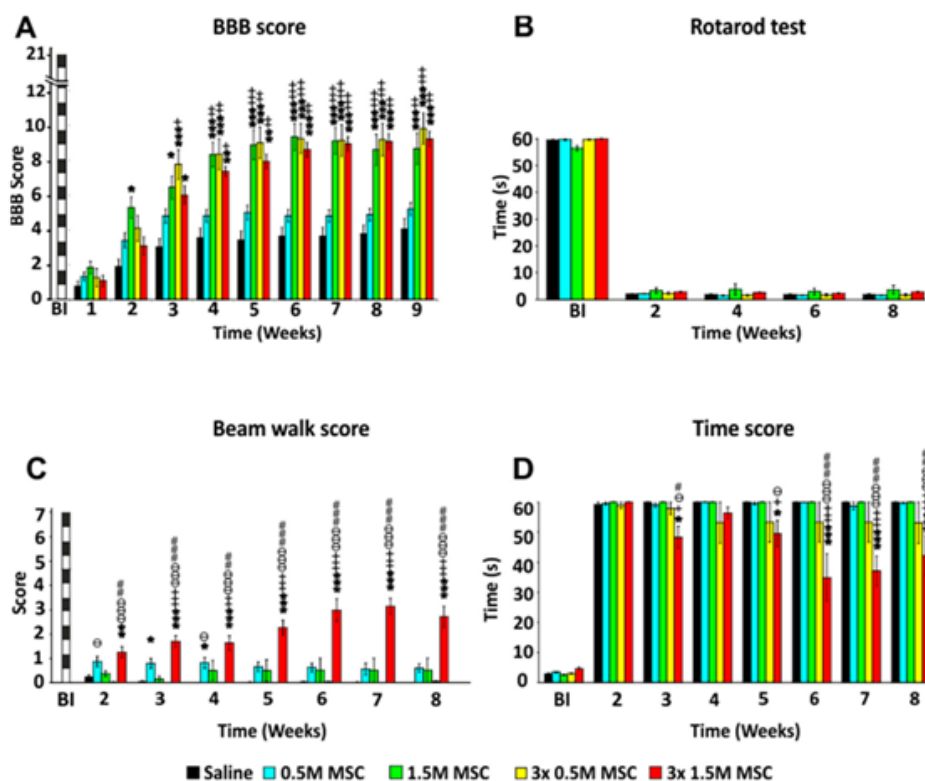


Figure 2: Hind leg motor function recovery after hWJ-MSC implantation following SCI. The locomotive function of both saline treated and hWJ-MSC treated rats were assessed with a BBB score (A), rotarod test (B), beam walk score (C), and time score (D). BBB score shows significance between higher and repeat doses when compared to saline control and 0.5 M MSC treatment. The Rotarod test, which assesses strength and limb coordination, showed no significance. Advanced locomotive skills during the beam walk score showed significant improvements for the 3 × 1.5 M MSC treated rats. 3 × 1.5 M MSC treated rats showed a significant time improvement for crossing the beam when compared to other treatments [21].

Clinical trials also show significant improvements in SCI rehabilitation after WJ-MSC implantation. In a study conducted by Albu and colleagues, neurosensory and neuromuscular responses were compared before and after treatment of a single dose injection of WJ-MSC (10×10^6 cells). No significant side effects were determined during the randomized, double-blind, crossover, placebo-controlled clinical trial. As a phase 1/2 clinical trial, 10 participants with a complete chronic SCI were recruited. Participant SCIs were ranked A on the American Spinal Injury Association scale and were located from T1-12. It was found that there was a significant increase in the dermatome pinprick sensation below the level of injury after implantation of WJ-MSC and individual responses to bladder maximum capacity, bladder hyperactivity, and external sphincter dyssynergia. No significant results were found for motor function, spasticity, MEPs, SEPs, bowel function, quality of life, or independence measures were found [24].

A similar study was conducted by Shim and colleagues during a randomized, open-label, phase I/IIa clinical trial. This study evaluated the effectiveness, practicality, and safety of WJ-MSC and teriparatide on Osteoporotic Vertebral Compression Fracture (OVCF) management. 20 subjects received either teriparatide alone as the control or combined WJ-MSC and teriparatide treatment. Teriparatide treatment involved 20 µg/day, daily subcutaneous injection for the entire study duration. WJ-MSC treatment included intramedullary (4×10^7 cells) injection and intravenous (2×10^8 cells) injection after 1 week. 6 of the subjects were unable to complete follow-up assessments due to adverse treatment reactions and other medical complications. Despite the subject improvement in the control group, statistical significance was observed on the VAS pain scale, ODI disability index, and SF-36 scores during the study period. No statistical difference was found for bone turnover markers, and no significance was determined between the two treatment groups when measuring bone mineral density. Bone mineral density was, however, improved significantly for both the experimental and control groups (Fig. 3) [25].

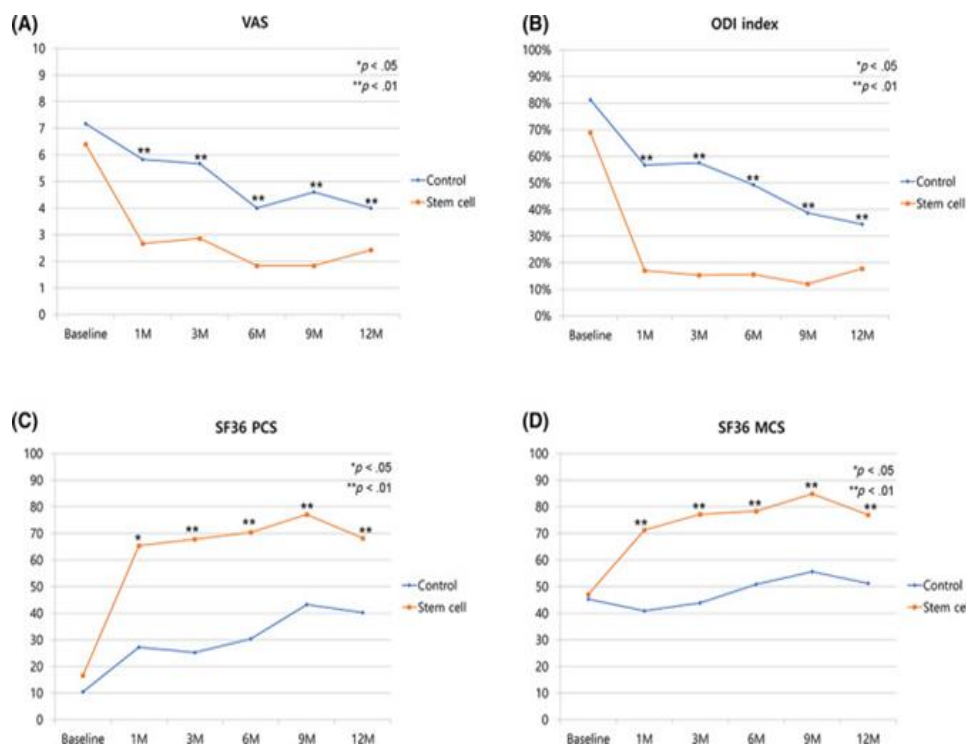


Figure 3: VAS pain scale (A), ODI index (B), and SF-36 (C)(D) were assessed for both the control group and WJ-MSC treated group over 12 months. SF-36 PCS measured the physical component, while the SF-36 MCS measured the mental component of the evaluation. VAS, visual analog scale. ODI, Oswestry disability scale. SF, short form. PCS, physical component summary. MCS, mental component summary [25].

Umbilical Cord Blood Stem Cell Therapy

While the presence of Haematopoietic Stem Cells (HSC) in umbilical cord blood has been extensively studied, MSC isolation from human umbilical Cord Blood (hCB) is a more recent topic of interest. hCB-MSC extraction has faced experimental restrictions due to the lower presence when compared to BM-MSC. The lower quantities of hCB-MSC are further congruent with adult peripheral blood stem cell collection (PB-MSC), and it additionally appears that preterm hCB is richer with MSC than term hCB [26,27,28]. Despite the apparent deficiency of hCB-MSC, isolation is shown to be successful. Neuroglial differentiation, in particular, was demonstrated in a study on the multipotency of hCB-MSC. After hCB collection, the expression of neural markers has been identified. These markers include nestin, neurofilaments, Glial Fibrillary Acidic Protein (GFAP), and tyrosine hydroxylase. Despite the overall lower hCB-MSC isolation levels, these MSC have been shown to also have a greater expansion potential when compared to BM-MSC [29].

With therapeutic potential, animal models have been used to determine the effectiveness of hCB-MSC SCI treatment. Nontraumatic SCI, such as Amyotrophic Lateral Sclerosis (ALS) has been studied as a potential target for hCB stem cell therapy [30]. An example of this is a study conducted by Ende and colleagues to evaluate the effects of human umbilical cord blood treatment on amyotrophic lateral sclerosis in diagnosed sod mice. Mutagenic sod mice, which contain a human transgene mutation of the SOD1 gene, were first assessed for their normal lifespan as a negative control. Normal sod mice have an average lifespan of 130 days due to irradiation paralysis. The transgenic mice were first divided into three treatment groups. 23 mice were initially present during the study but died prior to paralysis onset. 4 of the remaining mice (Group 1) were randomly selected and designated as the control group. No evidence of paralysis was observed at 8 weeks, and no treatment was given to the control group. 6 of the mice (Group 2) were treated with 0.1 mL Anti-Asialo GM1 antikerler sera 24 hours prior to irradiation treatment. After the waiting period, the Group 2 mice received 800 cGy of Cs 137 irradiation. Irradiation exposure was consecutively followed by a transfusion of nucleated cells isolated from the bone marrow of WT congenic mice. The remaining 11 mice (Group 3) received 800 cGy of irradiation 24 hours after a 1cc anti-killer sera injection. Treatment was followed with a transfusion of CB mononucleated stem cells. Group 3 mice, treated with hCB stem cells, had the greatest lifetime increase. Only 5 out of 11 of the mice were dead by day 140, and human DNA was found in 4 of the Group 3 treated mice. Less significance was

found with the BM treated mice. In this Group 2 treatment, all but 1 of the mice were dead by day 140. For negative control comparison, the Group 1 mice were all dead by day 130 after showing paralysis by day 115. This followed literature research and confirmed the significance of the hCB treatment group. The Ende and colleagues study confirmed the potential of ALS treatment with hCB stem cells in the mouse model [31].

Another animal model study was conducted by Dasari and colleagues to determine the spinal cord injury functional recovery of rats when treated with umbilical cord blood stem cells. Preliminary motor and balance functions were initially assessed for later comparison. The evaluation included a BBB locomotive test, a narrow-beam crossing, and a contact placement response evaluation. On days 1 and 2, after a moderate SCI induction via a weight drop device (NYU Impactor), behavioral tests were performed. Evaluations were then performed subsequently once every 5 weeks. The study found that hUCB-MSCs reduced post-traumatic apoptosis, promoted the upregulation of survival proteins, preserved cytoskeleton integrity of the damaged spinal cord, and significantly improved locomotive function when compared to untreated rats (Fig. 4) [32].

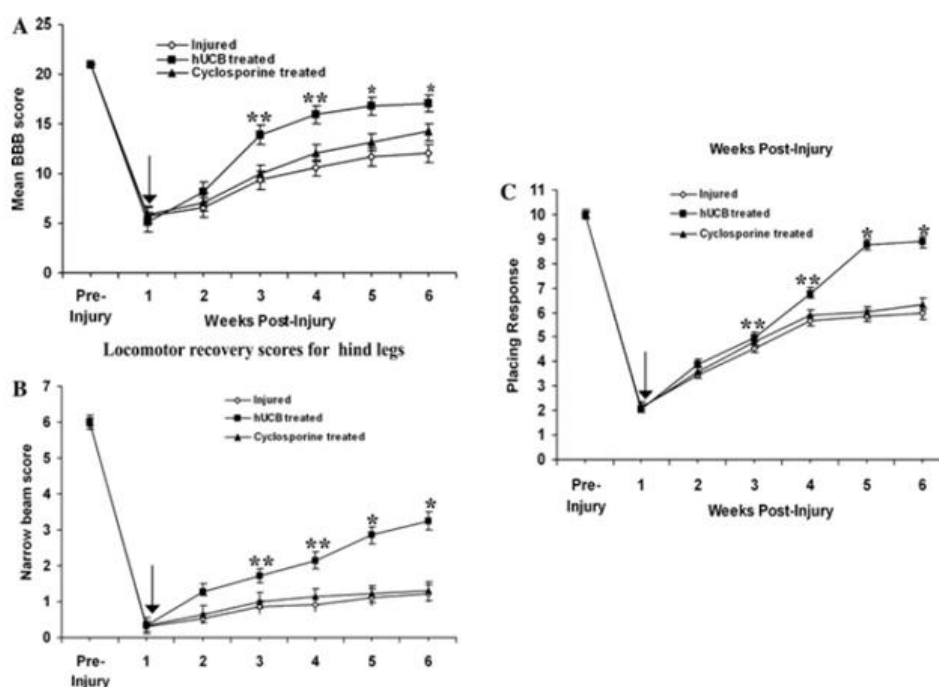


Figure 4: BBB test (A) measured functional recovery of hind-limb function with a maximum score of 21. Narrow-beam crossing exam (B) assessed the completion of crossing a 30 cm beam. Points were additionally determined by the proper placement of hindlimbs. Crossing placing response (C) evaluated placing responses of the dorsal foot without joint displacement. All trials showed significant differences in the treatment group by the end of the 6-week evaluation period [32].

Aside from animal models, clinical trials also provide support for the effectiveness of umbilical cord blood during spinal cord injury therapy. While there is a lack of clinical trials provided for hCB-MSC treatment, transplantation is a supported method regarding safety and primary efficacy [33,34]. During one such study by Yao and colleagues, 25 subjects participated in a human umbilical cord blood stem cell transplantation -through both lumbar puncture and intravenous administration- to evaluate its long-term effects during long-term spinal cord rehabilitation. Another 25 participants served as a control group and did not receive hCB treatment. Treatment results were evaluated pretreatment, at 6 months, and 12 months. At a mean time of 6 months, the treated group was determined to have a statistically significant latency time on both left and right lower limbs when compared to pretreatment. While there was no overall significant difference in ASIA sensory and motor score after stem cell therapy, autonomic functional improvements can be seen. Symptoms of treatment were marginal, and no severe complications were present, however, treatable side effects -such as headaches and externally controlled fevers- were observed in early treatment stages. The clinical trial overall concluded that hCB stem cell therapy is both a safe and effective long-term treatment (Table 2) [35].

Index	Spinal cord injury			Total
	Cervical	Thoracic	Lumbar	
Improvement in ASIA score	1(4)	2(8)	1(4)	4(16)
Decrease in spasm	3(12)	4(16)	0(0)	7(28)
Improvement in autonomic function	2(8)	4(16)	2(8)	8(32)
Improvement in urinary function	1(4)	3(12)	2(8)	6(24)
Improvement in SSEP test	2(8)	5(20)	2(8)	9(36)

Table 2: Amount and percentage of functional recovery was calculated as a percentage [n(%)]. n=25. ASIA score compliance was held with the International Standards for Neurological Classification of Spinal Cord Injuries. SSEP: somatosensory evoked potential [35].

There have additionally been implications of cytokine production from human umbilical cord blood cells, which can potentially hold recovery benefits for secondary mechanisms during SCI [36,37]. One particular study looked at cytokine production from hCB-MSC in varying culture conditions. Samples followed an antibody-based protein array and Immunophenotyping protocol for cytokine production comparison. It was found that hCB produces IL-6, IL-8, and MCP-1 in abundance, all of which help with immunological reactions. Further analysis showed that, unlike BM-MSC, hCB does not produce G-CSF. TIMP-1 and TIMP-2 Extracellular Matrix (ECM) remodeling proteins could also be observed in hCB-MSC expression. Altogether, these factors indicate that umbilical cord MSCs have a cytokine presence that can prove to be beneficial to SCI rehabilitation [38].

Study Limitations and Future Directions

While there are many therapeutic benefits to hCB-MSC treatment, there are a few clinical restrictions that can stagnate updated research. An illustration of treatment limitations includes potential scarring and compression from chronic intrathecal infusions of rats with spinal cord injuries. In this study conducted by Jones and Tuszyński, the secondary damage from the intrathecal catheter was evaluated over 2 weeks. Histology and immunocytochemistry results confirmed the secondary damage [39]. Intrathecal administration of stem cells was additionally discouraged during spinal cord inflammation treatment due to its ability to entrap grafted cells in the pia mater of the spinal cord in rats [40]. Aside from possible damage during transfusion, side effects can additionally present during treatment. Possible symptoms include headaches, fever, and lumbago. These side effects typically self-resolve after the first weeks of treatment, and adverse side effects are not observed [33,41]. Another limitation to the data collection of SCI treatment utilizing hUC-MSC therapy is the lack of data on nontraumatic SCI. As mentioned, nontraumatic SCI is becoming increasingly prevalent in American society due to the increase in the geriatric population and remains more prevalent than traumatic SCI [4]. This places a large emphasis on the need for new preliminary and clinical trials of nontraumatic SCI MSC therapy. The animal model methods behind UC-MSC treatments of ALS should, therefore, be applied to other nontraumatic spinal cord injuries. The lack of information on hUC-MSC treatment on nontraumatic SCI is highlighted by an overall lack of human clinical trials. Multiple animal trials have provided evidence for inflammation regulation, neural differentiation, reduction of apoptosis, and self-renewal properties of human umbilical cord cells [21-23,30,31,42,43]. These promising preliminary results have been carried over to clinical trials, though in a limited manner. Results are variable and appear to be dependent on administration method and dosage [45,46]. Clinical trials are further restricted as a result of the number of participants, ethical limitations, and logistics. Phase III trials are especially limited, as there is a lack of established UC-MSC protocols [46,47]. Current ongoing trials can be seen below in Table 2 [48].

Ongoing Clinical Trials

Table 3 Current clinical trials of umbilical cord stem cell therapy for spinal cord injury treatment. Data was found using NIH U.S. National Library of Medicine [48].

Identifier	Enrollment Status	Primary Investigator	First Posted	Description	Administration Method	Phase	Estimated Enrollment
NCT05152290	Recruiting	Limin Rong, M.D.	12/9/2021	Study the efficiency and safety of cultured UC-MSC for the treatment of SCI	Intravenous infusion and intrathecal injection (100 million cells total)	I	20
NCT03521323	Recruiting	Limin Rong, M.D.	05/11/2018	Study the efficiency and safety of UC-MSC for the treatment of early-stage SCI	Intrathecal Transplantation	II	66
NCT03505034	Unkown	Limin Rong, M.D.	04/28/2018	Study the efficiency and safety of UC-MSC for the treatment of chronic SCI	Intrathecal Transplantation	II	43
NCT03521336	Unknown	Limin Rong, M.D.	05/11/2018	Study the efficiency and safety of UC-MSC for the treatment of sub-acute SCI	Intrathecal Transplantation	II	84
NCT01393977	Unknown	An Yihua, doctor	07/14/2011	Comparison between rehabilitation and UC-MSC transplantation for patients with SCI in China	Lumbar puncture	II	60
NCT03979742	Recruiting	Bobo Chen, PhD	07/07/2019	UC-MSC transplantation followed by locomotive training for 3-6 months	Transplant above and below injury site (4 injections, 100,000 cells/ μ L)	II	18
NCT04213131	Unknown	Jing Liu, PhD	12/30/2019	Study the efficiency and safety of UC-MSC and UCB-MSC for the treatment of chronic SCI	Intravenous administration (5×10^7 hUC-MSCs/100 mL), lumbar puncture (5×10^7 hUC-MSCs/5 mL w/ 5mL CSF)	N/A	42

Table 3: Ongoing clinical trials.

Conflict of Interest

The authors have no conflict of interest to declare.

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