



It is Time for More Research into Umbilical Cord Stem Cells as a Potential Treatment in Neurological Diseases

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ABSTRACT

Umbilical cord stem cells (UCSCs) from newborn individuals have been widely used to treat blood and immune disorders. In recent years, many public and private cord blood banks have preserved UCSCs in the hope of using them to cure diseases, especially neurological conditions. Preclinical studies showed UCSCs have considerable regenerative potential and early clinical investigations demonstrated they are safe and effective. Here, we discuss the characteristics and clinical application of UCSCs as a potential treatment for prevalent neurological disorders, based on published studies and ongoing trials registered in Clinicaltrials.gov. Despite the advantages of

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UCSCs compared to other stem cell sources, few published randomized and controlled clinical studies have investigated their therapeutic potential in neurological disorders, including cerebral palsy and spinal cord injury, with interesting results. Thus, there is an urgent need for more investigation, such as well-designed, phase II and III randomized and controlled clinical trials.

Keywords: Umbilical cord stem cells; umbilical cord blood; neurological diseases; cerebral palsy; spinal cord injury.

1. INTRODUCTION

Early preclinical and clinical data suggested umbilical cord stem cells (UCSCs) offered multifunctional benefits in stem cell-based therapies, including neurorestorative potential in central nervous system (CNS) dysfunctions [1-7]. Based on this, there was great hope of curing neurological disorders, which contributed to an increase in the collection and storage of UCSCs in public and private banks worldwide. Later, phase I and II clinical trials suggested promising new therapies, while, at the same time, new questions and challenges arose, such as that of elucidating the action mechanisms that would explain the benefits described. As recent advances in preclinical studies also point towards several neurologic benefits, we urge the need for more clinical trials, in a wider range of institutions and countries, in an effort to develop UCSC-based treatments for neurologic diseases.

While promising results using stem cells from other neonatal birth-associated tissues have been reported to treat neurological conditions, cell availability could be a barrier to conduct further large trials. Thus, UCSCs remain as an easier and interesting option to the regenerative research.

Since 1988, hematopoietic stem cells from umbilical cord and placental blood of newborn individuals have been successfully collected and used in ~ 35,000 bone marrow transplants worldwide, to treat malignant and non-malignant blood and immune disorders, and also pediatric tumors [8,9]. This is a U.S. Food and Drug Administration (FDA) approved therapy, which puts this source a step ahead of the other sources of stem cells being explored for cell therapy and regenerative medicine approaches [10]. Umbilical cord blood (UCB) is rich in hematopoietic stem cells, and also contains non-hematopoietic cells including mesenchymal stem cells (MSCs), unrestricted somatic stem cells and endothelial progenitor cells. MSCs can also be found in large quantities in umbilical cord tissue,

more precisely in the Wharton's jelly and perivascular regions of the umbilical cord [11-17]. In recent years, many public and private cord blood banks have preserved UCB and umbilical cord tissues, facilitating clinical access worldwide [11,18,19].

UCB possesses unique advantages, including easy collection, minimal ethical concerns, low risk of transmitting infections due to collection timing, low immunogenicity, and immediate availability for usage, as it is collected and stored in liquid nitrogen [12,20]. Cells from UCB are also more immature and, therefore, have great proliferative potential and low immunogenicity, compared to other stem cell sources in adults [8,12,13]. Additional benefits are related to the immaturity of cells, which have longer telomeres - protecting them from premature loss of viability - and greater proliferative potential [8]. Perhaps the most important advantage is the higher tolerance of human leukocyte antigen (HLA) disparity, represented as a lower chance of rejection and lower incidence of severe graft-versus-host disease after UCB transplantation [17,21]. This is because UCB are enriched with regulatory T cells that suppress immune responses [21-23]. This could be especially interesting in the case of neurological diseases involving post-injury inflammation and immune-mediated causes [24-27]. Moreover, monocytes present in UCB have been implicated as important players in the brain after anoxic injury [28]. MSCs from umbilical cord tissue have a great capacity for differentiation into several tissue types, including cartilage, bone, tendon, adipose and neural tissues [29,30]. This provides us with another opportunity to treat neurological disorders [31-33].

The disadvantages described are mostly related to UCB transplants, when the purpose is to repopulate the entire bone marrow. Cell dosage and the possibility of delayed engraftment represent the main challenges. Thus, efforts are underway to develop more efficient strategies for hematopoietic cell expansion and homing, increase the number of stem and progenitor cells

available and allow faster immune reconstitution after UCB transplantation [20,34,35].

In preclinical studies, UCB-based therapies have shown interesting regenerative potential. Immature cells from UCB are able to improve neural function, acting on proinflammatory cytokine clearance and remyelination in an aging brain in an experimental model of parabiosis [36]. Additionally, rats submitted to an intracerebral hemorrhage model exhibited significantly better motor function recovery after transplantation of UCB stem cells, associated with an increase in hepatocyte growth factor [21]. UCB-derived MSCs promote recovery of neurological function and angiogenesis in rats after cerebral ischemia/reperfusion, [37] and UCB stem cells administered intravenously reduce brain edema and improve neurological outcomes, while decreasing the inflammatory processes in a rodent model of ischemia [22].

Furthermore, a clinical trial conducted by Sun and co-workers in 2010 [38] demonstrated intravenous infusion of cryopreserved autologous UCB was safe and well tolerated in 184 children with cerebral palsy (CP) and other similar brain lesions. Years later, a Phase I clinical trial of autologous UCB infusions in 23 neonates with hypoxic-ischemic encephalopathy, also treated with cooling, demonstrated this approach was feasible and safe [39].

Besides UCB, MSCs from umbilical cord tissue are increasingly regarded as an alternative therapeutic option in neurological disorders due to several unique features, including their primitive nature and the ease with which they can be collected and isolated. Furthermore, MSCs are able to migrate to injured sites and promote regenerative and protective actions through immunoregulatory paracrine signaling and cell differentiation/replacement [40,41].

Umbilical cord-derived MSCs and their secreted factors are able to potentiate proliferation and differentiation of human neural progenitors *in vitro* and *in vivo* [42]. Due to their unique secretome, MSCs from umbilical cord are probably better for neurorestoration and proangiogenic activities than bone marrow-derived MSCs [43]. In a rodent model of spinal cord injury (SCI), umbilical cord-derived MSCs implanted at the site of the lesion improved locomotion and regeneration of corticospinal fibers, possibly due to the release of cytokines

and growth factors, and the modulation of microglial and astrocytic activities [7].

To analyze the “state of the art” in the field, we performed a literature review at the clinical level (published randomized and controlled clinical trials) to find the results related to UCSCs therapies in neurological disorders. The initial search in Pubmed, Embase and the Cochrane Library identified 1194 potentially relevant studies, 63 of which were considered for full reading. However, only three studies had a true randomized and controlled clinical trial design.

The first article, entitled “*Umbilical Cord Blood Therapy Potentiated with Erythropoietin for Children with Cerebral Palsy: A Double-Blind, Randomized, Placebo-Controlled Trial*” used unrelated allogeneic UCB to treat children with CP. The study combined erythropoietin (EPO) therapy with stem cells from UCB, in the hope of enhancing cell therapy efficacy. The UCB units selected for the study presented a minimum of 3.0×10^7 total nucleated cells / kg, and matched at least four of the six markers of HLA: HLA-A, HLA-B and HLA-DRB1. There were three groups of patients: pUCB group (received a single intravenous infusion of UCB with recombinant erythropoietin (rhEPO) and rehabilitation), EPO group (received a single intravenous infusion of placebo UCB with rhEPO and rehabilitation) and control group (received rehabilitation only). The pUCB group showed greater improvements than in the EPO and control groups ($p < 0.01$ for Gross Motor Performance Measure (GMPPM); $p < 0.008$ for Bayley Scales of Infant Development-II (BSID-II) mental scale; $p < 0.002$ for BSID-II motor scale; $p < 0.013$ for social cognition of functional independence measure for children (WeeFIM). Noticeable improvement was observed in [18] D-fluorodeoxyglucose positron emission tomography compared to the baseline [44].

The second study, from the same research group, entitled, “*Involvement of Immune Responses in the Efficacy of Cord Blood Cell Therapy for Cerebral Palsy*” also investigated the role of UCB in CP. It is a placebo-controlled, double-blind trial that used allogeneic UCB to treat patients with CP. Initially, 36 patients were enrolled, of whom 34 completed all tests and were divided into two groups: UCB group and control group. UCB units selected for infusion could have up to 2 HLA disparities among HLA-A, B, and DRB1, and required at least 2.0×10^7 total nucleated cells/kg to be used in the patients. Outcome scores were analyzed within 1, 3 and 6

months, although some data were collected days after the first UCB infusion. The UCB group showed greater improvement than the control group in the Manual Muscle Testing (MMT) ($p < 0.05$) and Gross Motor Functional Measure (GMPM) ($p < 0.01$). BSID-II mental scale showed no significant difference, as did the WeeFIM. The pro-inflammatory markers pentraxin-3 (PTX3) ($p < 0.01$), toll like receptor-2 (TLR-2) ($p < 0.05$) and toll-like receptor-4 (TLR-4) ($p < 0.05$) were also modulated by UCB. As with the first study, neuroimaging data showed improved cortical activation in the UCB group compared to control [45].

The third trial, entitled "*Clinical observation of umbilical cord mesenchymal stem cell transplantation in treatment for sequelae of thoracolumbar spinal cord injury*" transplanted unrelated allogeneic MSCs from Wharton's jelly to treat subjects with thoracolumbar SCI. Two infusions of cultured stem cells were administered in two different loci in the spinal cord. Stem cells were previously expanded (6 to 8 passages) and submitted to flow cytometry for identification. A similar transplantation was repeated 10 days after the first infusion. Twenty-five microliters of cell suspension (4×10^5 cells / μL) were used in each injection. HLA testing was not mentioned, however, no major side effects were reported. Thirty-four patients were randomly divided into three groups: stem cell transplantation group (received two stem cells transplantations), rehabilitation therapy group (received functional recovery training and urinary retention training for 90 days), and a self-healing group (control). The transplanted group showed improvement in neurofunctional recovery compared to baseline at 6 months follow-up ($p = 0.012$ for motion, $p = 0.007$ for muscle tension and $p = 0.001$ for Barthel Index), as well as in urodynamic analysis ($p = 0.009$ for maximum bladder capacity and $p = 0.023$ for maximum detrusor pressure). Neither the rehabilitation group nor the control group exhibited any statistically significant improvement [46].

Currently, the public clinical trials database <http://www.clinicaltrials.gov/> shows there are 29 clinical trials using UCSCs to treat neurological dysfunctions. Most of these trials are safety studies (Phase I) and proof of concept (Phase II) with very few in Phase III (comparison of a new treatment to the standard treatment). To date, the results of some of the listed studies are yet to be published. For instance, a Phase II randomized placebo-controlled study is ongoing

at Duke University Medical Center, to access the efficacy of intravenous reinfusion of autologous cord blood for the treatment of pediatric patients with CP [47]. Among the clinical trials present in the database, some are being conducted to examine the role of autologous or allogeneic UCB and umbilical cord tissue-derived MSCs in the management of CP [9], amyotrophic lateral sclerosis (ALS; 1), stroke [12], SCI [7] and autism [4,8,12,15,20,48].

Despite the interesting potential of UCSCs shown in several studies, there is an urgent call for a larger number of studies worldwide and progression to phase III randomized controlled trials. From 906 potential studies about ALS, CP, stroke, epilepsy, SCI and encephalomalacia, only three were randomized controlled clinical trials using UCSCs. Although phase I and phase II clinical trials are underway, [8,12,15,20] more trials are needed to support the use of UCSCs in neurological diseases. While the body of results is limited, clinical data have demonstrated UCSCs are safe and effective, encouraging larger UCSCs trials in neurology. It is also necessary to take into consideration that a certain number of clinical trials, currently in phases I and II, will soon enter phase III, which in time, will include randomization and larger numbers of patients.

Given the lack of effective treatment options in central nervous system injuries, there is a need for new therapeutic alternatives, since neurological disorders are permanently disabling, impairing daily social activities and quality of life. There are very few ongoing randomized controlled phase II and III clinical trials related to UCSC transplantation to treat genetic and acquired neurologic diseases, despite interesting preliminary results. At the same time, there is a need for answers to questions and challenges that are relevant to preclinical and clinical research in this field, such as: 1) defining of the optimum cell type; 2) whether to use autologous or allogeneic UCSCs; specifically, there are questions regarding cell survival, immunosuppressive therapy requirement and risk of graft-versus-host disease with allogeneic UCB cells; 3) route of administration; 4) the number of applications required; 5) cell dose; 6) cell survival and homing; 7) the use of different scaffold types; and 8) the mode of action of UCSCs at the injury site and in the surrounding tissue. Thus, we call on the international scientific community to further explore these questions involved in the therapeutic potential of UCSCs.

Table 1. Included trials characteristics

Author, Year	Neurological condition	Transplantation type (Groups)	Cells characterization (Flow cytometry)	HLA-match test	Total cell infusion	Route of administration	Evaluated outcomes
Min et al., 2013	Cerebral palsy	3 groups: a) Unrelated allogeneic UCB + rhEPO + rehab; b) Placebo UCB + rhEPO + rehab; c) Placebo UCB + placebo rhEPO + rehab.	Not mentioned	Matched for at least four of six HLA types A, B, and DRB1	3×10^7 total nucleated cells/Kg	Intravenous	GMPM, GMFM, BSID-II, WeeFIM, 18F-FDG-PET/CT
Kang et al., 2015	Cerebral palsy	2 groups: a) Unrelated UCB; b) Placebo.	Not mentioned	Matched for at least four of six HLA types A, B, and DRB1	$\geq 2 \times 10^7$ total nucleated cells/Kg	Intravenous or intra-arterial	MMT, GMFM, GMPM, BSID-II, WeeFIM, PEDI, 18F-FDG-PET/CT
Cheng et al., 2014	Spinal cord injury	3 groups: a) Unrelated MSCs (from Wharton's jelly); b) Rehab therapy; c) Control (no intervention).	Levels of CD105, CD90, CD73 and CD44 higher than 95%; whereas CD19, CD45, CD11b or CD34 lower than 5%	Not mentioned	4×10^7 cells	Injected into perilesional spinal cord parenchyma	Sensation, motion, muscle tension, Barthel Index and urodynamics

Legends: UCB: umbilical cord blood; rhEPO: recombinant erythropoietin; HLA: human leukocyte antigen; rehab: rehabilitation; GMPM: Gross Motor Performance Measure; GMFM: Gross Motor Function Measure; MMT: Manual Muscle Testing; BSID-II: Bayley Scales of Infant Development-II; WeeFIM: Social Cognition of Functional Independence Measure for Children; 18F-FDG-PET/CT: 18D-Fluorodeoxyglucose Positron Emission Tomography; PEDI: Pediatric Evaluation of Disability Inventory. Cell culture conditions in Cheng et al., 2014: α -MEM containing 10% fetal bovine serum at 37 °C in an incubator (5% CO₂) for 10 days

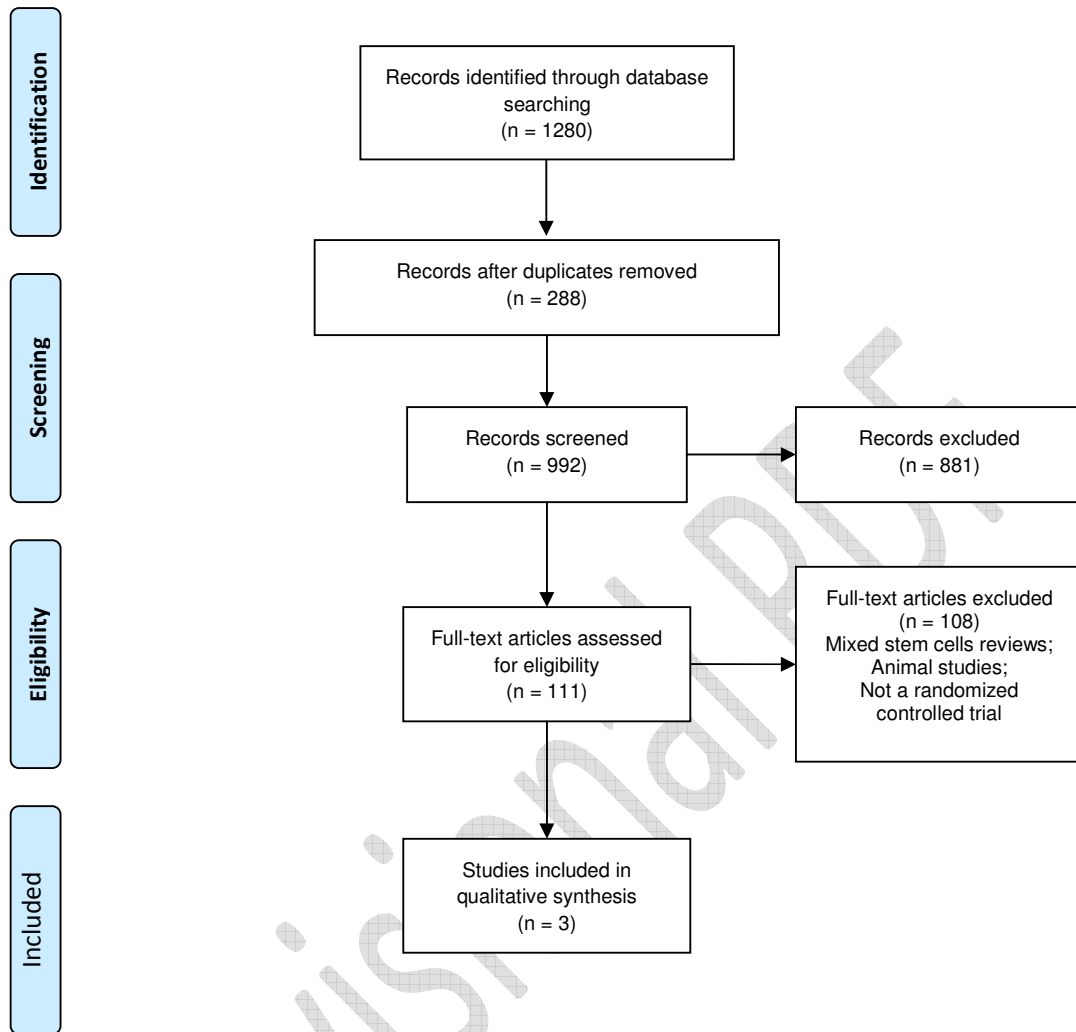


Fig. 1. Flowchart showing the selection process of the randomized clinical trials

2. CONCLUSION

The current lack of well-conducted randomized controlled trials investigating UCSCs and the absence of curative therapies for most neurological conditions suggest the need for further preclinical and clinical trials into this subject, since such neurological conditions are a serious public health issue. The establishment of safe and effective cell-based therapies using UCSCs could provide additional tools to aid restoration of motor and/or cognitive functions and to enhance the patient's quality of life.

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CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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