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Upcycling Umbilical Cords: Bridging Regenerative Medicine with Neonatology

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Abstract

Preterm birth is a major health concern that affects 10% of all worldwide deliveries. Many preterm infants are discharged from the hospital with morbidities that lead to an increased risk for neurodevelopmental impairment, recurrent hospitalizations, and life-long conditions. Unfortunately, the treatment of these conditions is palliative rather than curative, which calls for novel and innovative strategies. Progress in regenerative medicine has offered therapeutic options for many of these conditions. Specifically, human umbilical cord mesenchymal stem cells (MSCs) and cord blood (UCB) cells have shown promise in treating adult onset diseases. Unlike bone-marrow and embryonic derived stem cells, umbilical cord-derived cells are easily and humanely obtained, have low immunogenicity, and offer the potential of autologous therapy. While there are several studies to uphold the efficacy of umbilical cord MSCs in adult therapies, there remains an unmet need for the investigation of its use in treating neonates. The purpose of this review is to provide a summary of current information on the potential therapeutic benefits and clinical applicability of umbilical cord MSCs and UCB cells. Promising preclinical studies have now led to a research movement that is focusing on cell-based therapies for preterm infants.

Keywords

Mesenchymal stem cells; umbilical cord blood; bronchopulmonary dysplasia; hypoxic ischemic encephalopathy

INTRODUCTION

Preterm birth is a major worldwide concern that affects 10% of all deliveries and produces a vast economic burden.[1] Due to advances in neonatal medicine, survival rates for smaller and more preterm infants have improved. However, many of these preterm infants are discharged from the hospital with co-morbidities that lead to increased risk for neurodevelopmental impairment, recurrent hospitalizations, and life-long medical

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conditions. Unfortunately, current methods of treatment for these diseases are mostly palliative rather than curative. As such, there is an unmet need to establish new effective strategies that will target major neonatal diseases.

Recent developments in stem cell research may offer a new strategy to alleviate neonatal morbidity. Particularly, the literature focuses on mesenchymal stem/stromal cells (MSCs) and umbilical cord blood (UCB) as promising therapeutic agents because of their ease of isolation and release of biologic factors shown to protect and heal injured tissues.[2] Preclinical studies have now demonstrated that MSCs and UCB provide encouraging results in an array of adult morbidities, including autoimmune, neurodegenerative, and cardiovascular diseases.[3–6] Although many studies have shown the beneficial effects of umbilical cord-derived cells in the regeneration of adult disease, there is a lack of literature regarding their use in treating neonatal diseases.

Evidence suggests that the perinatal period offers a single opportunity for a non-invasive retrieval of MSCs and UCB. Precisely, the umbilical cord provides a rich source of MSCs, hematopoietic stem cells, progenitor cells, and mononuclear cells that are hallmarked for their high cellular proliferative rates, vast capacity for multi-lineage tissue differentiation, as well as their ability to negate immunologic rejection by administration of autologous cells.[7–10] Umbilical cord blood and Wharton's jelly-derived MSCs have translated into the clinics, as currently more than 130 clinical trials are registered utilizing these agents. Thus, the aim of this work is to provide an overall review of umbilical cord-derived cells and their potential therapeutic use in neonatal medicine.

DEFINING REGENERATIVE MEDICINE AND STEM CELLS

Regenerative medicine is an emerging field that utilizes cells and/or biomaterials to repair and restore the normal function of injured cells, tissues, and organs.[11] This area of translational research has received much public and media attention owing to its unique use of primitive and highly capable cells commonly referred to as stem cells.

A stem cell is defined as a cell that has the ability to self-renew as well as differentiate into specialized tissue cells.[12] They are responsible for giving rise to all the cell types (>200) that comprise the human body. Self-renewal occurs when the parent stem cell can mitotically divide into a daughter cell that maintains the same undifferentiated state.

Stem cells are categorized according to their plasticity. Briefly, embryonic stem cells can become any tissue cell type because they are pluripotent, while adult stem cells (also known as somatic stromal cells) have multipotent capabilities. Adult stem cells can be isolated from many tissue sources and then depending on the source can be specialized into ectodermal, mesodermal, or endodermal lineages. This review article will focus on multipotent adult stem cells derived from the umbilical cord Wharton's jelly and will close with a brief discussion of umbilical cord blood progenitor/mononuclear cells.

BENEFITS OF ISOLATING UMBILICAL CORD STEM CELLS

One of the advantages of upcycling umbilical cordsis the ability to isolate a variety of different cells (refer to Figure 1).. For instance, the umbilical cord blood can yield blood progenitor/mononuclear cells and hematopoietic/mesenchymal stromal cells, while the Wharton's jelly (the protecting tissue surrounding the umbilical vessels) can provide mesenchymal stem cells.[7] Additionally, umbilical cord perivascular/endothelial cells can be obtained for studies focusing on angiogenesis. Several methods have been described for the isolation of mesenchymal stem cells from the umbilical cord. The two most common techniques used to collect MSCs from Wharton's jelly includes an enzymatic digestion or explant culture.[13,14]

The isolation of mesenchymal stem cells from the umbilical cord blood or Wharton's jelly is valued because of its non-invasive and non-controversial collection from tissue that traditionally has been discarded as medical waste.[2] Evidence suggests that umbilical cord-derived MSCs have higher proliferative rates and lower immunogenicity compared to adult tissue stem cells.[15] This is due in part to their lack of MHC class I and low level of MHC class II expression.[16] Unlike embryonic stem cells, transplantation of human umbilical cord-derived MSCs have not shown an increased risk for teratoma formation.[17] Most importantly, cord MSCs and UCB cells can be isolated, propagated, and in the future autologously transplanted.

THERAPEUTIC PROPERTIES OF MSCs

Homing capacity

Homing to sites of injury and inflammation are among the appealing properties of MSCs. Similar to immunologic cells, MSCs express many of the cell surface receptors that are involved in endothelial attachment and migration into tissues.[18] Although the exact mechanisms are unknown, researchers have found that MSCs can transmigrate from the bloodstream to areas of tissue injury.[19–21] Upon arrival to the target tissue, MSCs differentiate into injured cell types and release soluble factors that promote tissue regeneration.

Studies involving vascular formation after tissue injury have discovered that vascular endothelial growth factor (VEGF) plays a critical role in the migratory patterns of MSCs.[22] The upregulation of VEGF stimulates MSC homing through interactions with stromal cell-derived factor-1 (SDF-1), a chemokine expressed after inflammation/injury.[23] The chemokine receptor CXCR4 complexes with SDF-1 to signal MSC migration as well as differentiation.[24] The ability to mobilize to sites of tissue damage have driven the interest of cell-based therapy in medicine.

Paracrine release of biologic factors

MSCs communicate with nearby cells by adapting to changes in their microenvironment. Initially, the therapeutic effects of MSCs was thought to be due to cellular engraftment into the wounded tissue. Studies have now confirmed that only a small percentage of MSCs

engraft.[25,26] Instead the beneficial properties of MSCs are now widely accepted as paracrine in nature.[27,28]

Secreted biologic factors have been identified in the media used to propagate the MSCs, also referred to as conditioned media.[29]. Preclinical studies in models of acute lung injury and skin injury have demonstrated similar efficacy between transplanting stem cells versus conditioned media without cells.[30,31] In addition to biologic factors, MSCs can also secrete extracellular vesicles that contain RNA or membrane proteins that function in intercellular communication and signaling.[32] Furthermore, researchers have also demonstrated mitochondrial transfer from umbilical cord MSCs to damaged cells.[33]

Antioxidant effects

Oxidative stress is characterized by a cellular imbalance between reactive oxygen species and anti-oxidants. Reactive oxygen species (ROS) present an important role in cell signaling, cell membrane and gene integrity, and more importantly they can function as regulators of cell death.[34] It has been reported that the overproduction of ROS (or underproduction of anti-oxidants) is linked to the pathophysiology of many medical conditions. Despite this, new evidence reveals that the interaction between ROS and exogenous administration of MSCs is reassuring.

Studies involving renal injury uncovered that MSCs advance the production of anti-oxidative molecules, depress renal tubular damage, and suppress renal cell apoptosis.[35] Similarly, in a cardiac study of ischemic-reperfusion MSC extracellular vesicles restored energy levels, recovered biomolecules in redox reactions, and reduced oxidative stress.[36] Arslan's study of myocardial ischemic-reperfusion injury in mice attributed the anti-oxidant effects through the activation of the PI3k/Akt pathway.[36] These studies provide evidence that MSCs and their paracrine secretions are useful agents in oxidative stress-induced tissue damage.

Angiogenesis

Many pharmacologic therapies have targeted the formation of new blood vessels (angiogenesis) to ameliorate vascular disease. Cell-based studies have supported this concept by reinforcing the normal development, growth, and repair of blood vessels as a therapeutic mean in ischemic vascular events. Examples of angiogenic effects of MSCs have been well established in experimental studies of peripheral vascular disease as well as tissue wound healing. For instance, Liang *et al* demonstrated new blood formation and production of vascular growth factors after MSC administration in a rat model of diabetic peripheral vascular disease.[37] Following cell transplantation, the animals had increased blood flow, limb function, and skin wound healing. In a skin injury model comparison study between Wharton's jelly-derived MSCs with adipose-derived MSCs, the cord-derived MSCs had a greater expression of VEGF, angiopoietin-1, and tubule formation.[38]

Zhang and associates studied the production of angiogenic factors and cardiac vascular density in a rodent model of acute myocardial infarction.[39] The investigators concluded that animals treated with MSCs had increased expression of placental growth factor, enhanced vascular density, as well as higher left ventricular fractional shortening. These

findings uphold that stem cells play an important role in the growth and repair of blood vessels through the production of biologic factors that support angiogenesis.

Immune modulation

The inflammatory cascade plays a significant role in the development of many neonatal diseases. Considerable evidence suggests that MSCs mediate inflammatory pathways through direct cellular contact and indirectly through secretion of bioactive molecules. MSCs modulate key steps in both the innate and adaptive immune system through the release of anti-inflammatory factors such prostaglandin E, interleukin 10, and hepatocyte growth factor. These factors are known to regulate the activity of lymphocytes, natural killer cells, and macrophages. [40]

Exogenous MSC therapy has shown to decrease the proliferation of $CD4^+$ and $CD8^+$ T-cells. In an in-vitro study of umbilical cord MSCs, Vellasamy *et al* showed that T-cell proliferation is inhibited when exposed to direct cell-to-cell contact with MSCs.[41]. Interestingly, when compared to bone marrow derived stem cells, Wharton's jelly-MSCs had a greater ability to suppress T-cell activation and proliferation.[42]

In addition, Spaggiairi *et al* have also linked the suppression of natural killer cell proliferation with MSC administration.[43] When cultured with MSCs, NK cells had a reduced ability to secrete interferon gamma. In a co-culture study of NK cells and human bone-marrow MSCs, Sotiropoulou *et al* showed that MSCs inhibited NK cell proliferation, function, and phenotype.[44]

CLINICAL APPLICABILITY

Mesenchymal stem cells have emerged as novel biologic agents for numerous adult and pediatric illnesses. Their multifaceted properties make them attractive therapies to promote tissue healing. Although the largest push for their use in clinical trials has been in the adult population, recent trials have begun to target neonates. Despite comprising a targeted population, advances towards novel treatments is warranted since their prolonged hospital stay and multiple morbidities make these patients among the most expensive..

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic lung disease in premature neonates that is a result of prolonged oxygen and ventilatory support. This condition is characterized by impaired alveolar development and lung vascular growth. Infants diagnosed with BPD are at increased risk for neurodevelopmental impairment, recurrent hospitalizations, and long-term cardio-pulmonary morbidity.[45] Despite advances in neonatal medicine, few therapies have shown clinical efficacy in preventing or treating BPD.

Origins of BPD are often multifactorial involving triggers such as mechanical ventilation, inflammation, oxygen toxicity, infections, and genetics. After birth, extremely preterm infant lungs are exposed to inflammation from positive pressure ventilation, antioxidant stress from chronic hyperoxia, and poor lung growth and development secondary to abnormal

angiogenesis. Of all the neonatal conditions, BPD is at the forefront of translational studies incorporating regenerative research.

Preclinical studies

Cord MSC therapy is effective in improving alveolar development and vascular development in animal models of hyperoxia-induced BPD (Refer to Table 1). Intratracheal injection of 5×10^5 MSCs improved survival, weight gain, and decreased markers of inflammation in a rodent model of BPD.[46] Most studies attribute the positive findings to paracrine release of VEGF or hepatocyte growth factor, as engraftment of cells to lung tissue is low. Thebaud's research group showed long-term improvement in exercise tolerance and lung architecture after a single dose of MSCs in rats with BPD.[47]

As previously described, multiple studies show that the benefits of MSCs depend on the release of soluble factors that protect and heal alveoli and pulmonary vessels from injury. Most studies attribute the benefits of MSCs to treat neonatal chronic lung disease through its role in improved vascular growth and development. Studies using contrast imaging have clearly associated improved lung alveolarization secondary to the release of VEGF into the cellular environment.

Clinical studies

Just recently, scientists in South Korea completed the first phase I dose-escalation clinical trial of MSC therapy for preterm neonates at risk for developing BPD.[48] This study included 9 neonates between gestational ages 23 to 29 weeks and a birthweight of 500–1250 grams. Patients either received a low dose, defined as 1×10^7 cells/kg, or high dose (2×10^7 cells/kg) of allogeneic cord blood-derived MSCs. Administration of MSCs did not have any acute cardiopulmonary complications and although not powered to show efficacy did demonstrate a trend towards improving BPD severity as well as markers of systemic inflammation.

Despite these favorable findings, the molecular mechanisms that MSCs impact to regulate normal alveolar development in premature infants remains incompletely understood. Evidence does favor the theory that exogenous MSCs most likely provide benefit in BPD by rescuing endogenous lung stem cells. Collectively, use of MSCs for attenuating changes associated with BPD seems encouraging and open new prospects for regenerative medicine research. Further studies are required in this area to address key questions (optimal route, dose, frequency, timing) before undertaking any assertive measures.

UMBILICAL CORD BLOOD CELLS

Human UCB is rich in stem, progenitor, and mononuclear cells of hematopoietic lineage. Similar to adult stem cells, progenitor cells can differentiate into several cell types, but they are more lineage committed and have limited self-renewal.[55] The umbilical cord blood also contains a plentiful supply of mononuclear cells (T cells, B cells, and monocytes). Like Wharton's derived-MSCs, UCB cells have several advantages when compared to other sources of hematopoietic/progenitor cells: i) rapid proliferation, ii) decreased incidence of graft versus host disease, iii) simple retrieval, iv) can be easily processed and cryopreserved,

and v) contain higher number of immunologic cells.[10,56,57] However, one significant drawback to UCB is that the number of cells retrieved is low and often cord banks must pool multiple umbilical cords to obtain the desired yield.[58]

Hypoxic Ischemic Encephalopathy

Hypoxic ischemic encephalopathy (HIE), also known as perinatal asphyxia, is distinguished by neuronal cell death after a period of decreased/lack of blood flow and oxygen to the brain. In developed countries HIE affects approximately 1–5 neonates per 1000 live births and is the most common cause of neonatal seizures at birth.[49] Survivors from severe asphyxia are at increased risk for devastating outcomes including mental deficiency, life-long seizures, and cerebral palsy.[50] Even with rapid advances in perinatal care, the incidence of HIE has not changed.

Since most cases of HIE occur in-utero, treatment options are limited and focus on reducing the extent of initial brain injury. Infants with moderate to severe asphyxia undergo hypothermic therapy to decrease brain oxygen and energy requirements, reduce free radical expression, and diminish excitatory neurotransmitter release.[50] Nowadays, cell-based therapies have surfaced as future treatment options for infants with HIE.

Preclinical studies

In addition to improving lung injury, umbilical cord MSCs mediate improvements in cognition, motor-sensory ability, as well as infarct size in animal models of HIE. For instance, a single intraventricular dose of MSCs into a rat with a cerebral artery occlusion attenuated the lesion volume and improved survival rates after the brain injury.[51] Further supporting these findings, Zhang and Zhu have shown restoration of sensorimotor capacity and increase in precursor neuronal cells in rodents that received MSC administration.[52,53] Although the mechanism that underlies the restorative properties of MSCs for HIE treatment is still unknown, both reports attribute the homing properties, differentiation capabilities, and most importantly the expression of trophic factors that lessen inflammation as the source for organ recovery.

Clinical studies

Data for the first phase I clinical trial (NCT00593242) to evaluate the feasibility and safety of autologous cord blood cell infusions for moderate to severe HIE has been released.[54] Twenty-three infants received non-cryopreserved, volume- and red blood cell-reduced UCB and were compared to 82 infants who underwent conventional medical management. The study dose was substantially higher (5×10^7 cells/kg) than those used for the BPD trial and the majority of subjects received multiple infusions. This study showed that autologous cord blood transfusion is feasible, has a high recovery of viable cells, and did not result in significant adverse reactions. Preliminary neurodevelopmental outcomes in the subset of patients who received UCB therapy seemed propitious.

Hypoplastic left heart syndrome

Hypoplastic left heart syndrome (HLHS) is one of the most complex and deadly congenital heart diseases.[59,60] Typically, HLHS will require multiple staged surgical procedures to

correct the underdeveloped left side of the heart.[61] Even patients who survive the three major surgeries, have a significantly lower life expectancy.[60,62]

In the United States, five sites are currently conducting human clinical trials with regenerative cells for HLHS (clinicaltrials.gov). Mayo Clinic, University of Oklahoma, and Duke University are utilizing autologous umbilical cord blood cells. Most of the studies will be administering the cells directly to the right side of the heart during the first surgical repair. In Japan, the APOLLON clinical trial is in Phase III testing of autologous cardiac stem/progenitor cells for single ventricle disease. Furthermore, the TICAP (Transcoronary Infusion of Cardiac Progenitor Cells in Hypoplastic Left Heart Syndrome) trial in Japan demonstrated safety, improved right ventricle ejection fraction and decreased heart failure in a small cohort of neonates who received autologous heart progenitor cells. [63]

Intraventricular hemorrhage

Twenty five percent of very preterm infants develop spontaneous intraventricular hemorrhages (IVH). [64] The etiology of IVH is multifactorial and is potentiated by an immature vascular development in the germinal matrix, as well as rapid changes in cerebral blood flow. [65] Using an experimental model of severe IVH, Ahn *et al* demonstrate that administration of umbilical cord blood stem cells reduced hydrocephalus and improved behavioral testing.[66] The same team of investigators showed that only early transplantation of MSCs (two days after IVH induction) showed neuroprotection. [67] Recruitment is underway for patients with severe IVH (phase II trial)and intraventricular administration of UCB MSCs. The outcomes focus on death,ventricular shunt, as well as ventricular dilatation, and will incorporate magnetic resonance imaging at term equivalent.

CONCLUSION

The umbilical cord offers a vast supply of mesenchymal stem cells that can be aimed to treat neonatal diseases. Preclinical studies provide evidence for the remarkable properties these cells possess. Aside from improving inflammation and angiogenesis, umbilical cord cells can migrate and abate oxidant stress. Further research entailing safety and long-term effects are necessary before stem cell therapy becomes a clinical option for neonates. Some of the more important questions that need to be addressed include:

- WHO: Which patients are eligible for stem cell therapy?
- WHAT: Which cell population/cell derivative will provide the best clinical outcomes?
- WHEN: Should cells be given prophylactically or as rescue therapy?
- HOW: Which route and dose is most efficacious?
- WHY: What are the molecular mechanisms that cell-based therapies are targeting in neonatal disease?

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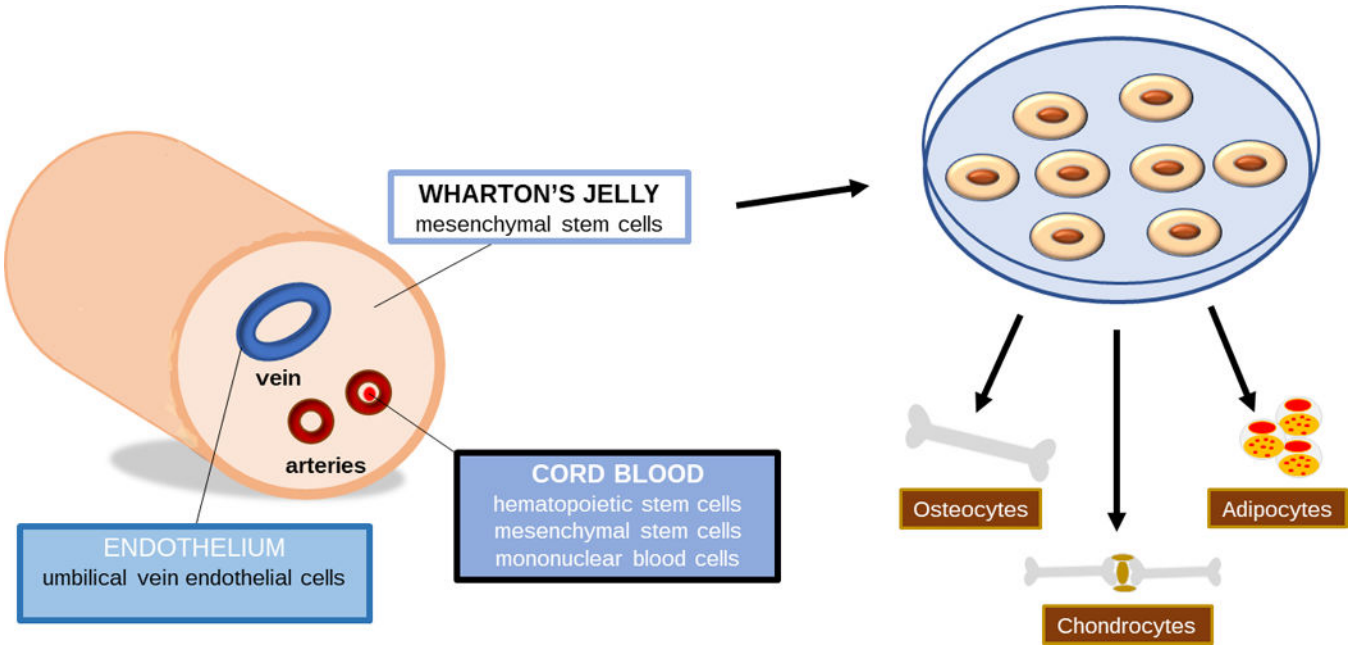

Figure 1.
Umbilical cord derived cells

Table 1.

Summary of preclinical studies of umbilical cord-derived MSCs to treat BPD

Source	Animal characteristics	Objective	MSC characteristics	Outcome
Author: Chang *et al*[46] **Year:** 2011	**Animal model:** Sprague-Dawley rat pups **BPD model:** 95% oxygen from birth to 14 days of age	Optimize dose of cord blood MSCs in attenuating BPD	**Source:** human umbilical cord blood **Dose:** Low: 5×10^3 MSCs; High: 5×10^4, or 5×10^5 MSCs **Delivery:** intratracheal at postnatal day 5	Improved lung architecture (per mean linear intercept), survival, and body weight gain in higher doses of MSCs Higher doses of MSCs decreased inflammatory cytokines: TNF-α, IL-1β, IL-6, and TGF-β Reduced oxidative stress in higher doses of MSCs
Author: Ahn *et al*[68] **Year:** 2015	**Animal model**: Sprague-Dawley rat pups **BPD model:** 90% oxygen from birth to 14 days of age	Determine the optimal cell type to protect against BPD	**Source:** human umbilical cord blood **Dose:** 5×10^5 MSCs **Delivery:** intratracheal at postnatal day 5	Decreased mean linear intercept in MSC group Inflammatory cytokines IL-1α, IL-1β, IL-6, and TNF-α Increased lung VEGF and HGF in MSC group
Author: Liu *et al*[69] **Year:** 2014	**Animal model**: Severe combined immunodeficient mice **BPD model:** 90% oxygen from birth to 7 days of age	Studied the morphologic and functional effects of intranasal vs. intraperitoneal administration of MSCs in BPD	**Source:** cord tissue MSCs **Dose:** Low: 1×10^5 MSCs; Mid: 5×10^5 MSCs; High: 5×10^6 MSCs **Delivery:** intratracheal at postnatal day 5	No significant changes in lung mechanics after MSC administration Histologic evaluation: • reduction in mean septal wall thickness in intraperitoneal administration of high dose MSCs • mean cord length was similarly reduced in high dose MSCs given via intranasal and intraperitoneal route
Author: Sung *et al*[70] **Year:** 2015	**Animal model**: Sprague Dawley rat pups **BPD model:** 90% oxygen from birth to 14 days of age	Determine the optimal route of MSC transplantation for BPD	**Source:** human umbilical cord blood MSCs **Dose:** Intratracheal: 5×10^5 MSCs; Intravenous: 2×10^6 MSCs **Delivery:** intratracheal vs. intravenous at postnatal day 5	MSC transplantation via both routes improved survival Greater decrease in mean alveolar volume in intratracheal delivery of MSCs; while mean linear intercept was similar between both experimental groups Genetic expression of inflammatory mediators was down-regulated in intratracheal MSCs but not intravenous Greater engraftment in intratracheal administration
Author: Pierro *et al*[47] **Year:** 2012	**Animal model**: Sprague Dawley rat pups **BPD model:** 95% oxygen from birth to 14 days of age	Determine if cell-based therapy is efficient and safe for treating BPD	**Source:** human umbilical cord blood MSCs, perivascular cells, conditioned media from both cell types **Dose:** 3×10^5 MSCs; 6×10^5 MSCs **Delivery:** intratracheal at postnatal day 4 (prevention) or day 14 (regeneration)	Short-term: MSCs, perivascular cells, as well as conditioned media from both cell types improved lung compliance and decreased mean linear intercept Conditioned media from MSCs and perivascular cells improved angiogenesis, but greater in perivascular cells Long-term: Exercise capacity improved after the following were given: MSCs, perivascular cells, and conditioned media of both cell types
Author: Chang *et al*[71] **Year:** 2013	**Animal model**: Sprague Dawley rat pups **BPD model:** 90% oxygen from birth to 14 days of age followed by 60% for 7 days	Determine the optimal timing for MSC transplantation to improve efficacy in BPD	**Source:** human umbilical cord blood MSCs **Dose:** 5×10^5 MSCs **Delivery:** intratracheal at postnatal day 3 (early), day 10 (late), or combination (day 13)	Survival rates were similar between control groups and hyperoxic animals that received MSCs at day 3 Mean alveolar volume was best maintained in early MSC delivery group

Source	Animal characteristics	Objective	MSC characteristics	Outcome
				Marker of oxidative stress was reduced in early, late, and combination therapy of MSCs Hyperoxia-induced decrease in lung HGF was upregulated in early and combination therapy
Author: Chang *et al*[72] **Year:** 2014	**Animal model**: Sprague Dawley rat pups **BPD model:** 90% oxygen from birth to 14 days of age	Examined whether VEGF secreted by MSCs plays a pivotal role in protecting against BPD	**Source:** human umbilical cord blood MSCs **Dose:** 1×10^5 MSCs, with/without VEGF **Delivery:** intratracheal at postnatal day 5	MSCs deceased mean linear intercept and mean alveolar volume BPD+MSCs demonstrated improved lung vascular formation VEGF knockdown decreased the regenerative properties of MSCs

MSC-mesenchymal stem cell; BPD-bronchopulmonary dysplasia; TNF-tumor necrosis factor; IL-interleukin; TGF-transforming growth factor; VEGF-vascular endothelial growth factor; HGF-hepatocyte growth factor

Table 2.

Summary of preclinical studies of umbilical cord-derived MSCs to treat HIE

Source	Animal characteristics	Objective	MSC characteristics	Outcome
Author: Zhu *et al*[53] **Year:** 2014	**Animal model:** 3-day old Sprague-Dawley rat pups **HIE model:** left common carotid artery ligation, followed by a 4-hour period of hypoxia with 6% oxygen	Effects of MSCs on behavioral function and glial cell function	**Source:** human umbilical cord blood **Dose:** 1×10^6 MSCs **Delivery:** intraperitoneal injection immediately after HIE, and then once/day for 3 days	Improved exploratory behavior and mental stress in HIE+MSC group Reduced asymmetry of forepaw preference in HIE +MSC group HIE+MSC group showed: • decreased loss of oligodendrocytes • decreased astrocyte proliferation
Author: Xia *et al*[73] **Year:** 2010	**Animal model**: 7-day old Sprague-Dawley rat pups **HIE model:** left common carotid artery ligation, followed by a 3-hour recovery period and 2.5-hour period of hypoxia with 8% oxygen	Investigate the effect of intracerebral transplantation of human cord blood-derived MSCs on HIE in rat neonates	**Source:** huma numbilical cord blood **Dose:** 1×10^5 MSCs **Delivery:** left cortical parenchymal injection 3 days after HIE	Nerve function improved after HIE+MSC injection
Author: Zhang *et al*[52] **Year:** 2014	**Animal model**: 7-day old Sprague Dawley rat pups **HIE model:** right common carotid artery ligation, followed by hypoxia for 2-hours at 8% oxygen	Potential therapeutic effect of Wharton's jelly MSCs in a rat model of HIE	**Source:** human Wharton's jelly MSCs **Dose:** 5×10^5 MSCs **Delivery:** 24 hour vs. 72 hour, jugular vein	afterE to evaluate neuroloical deficits HIE +MSC group had decreased escape latency in water maze test, higher rotarod latency, and Longa scoring (24 hour delivery with better results)
Author: Kim *et al*[51] **Year:** 2012	**Animal model**: 10-day old male Sprague Dawley rat pups **HIE model:** right middle cerebral artery occlusion at day 10	Determine the therapeutic efficacy of human umbilical cord-derived MSC transplantation in attenuating the severe brain injury induced by MCAO in newborn rats	**Source:** human umbilical cord blood MSCs **Dose:** 1×10^5 MSCs **Delivery:** intraventricular 6-hrs after MCAO	Longa scoring was performed at 6 hr, 7 days, 20 days afterHIE to evaluate neurolocal defi Mild improvement in sensorimotor testing Lesion size was smaller in HIE+MSC Double survival rates at one month in HIE+MSC group

MSC-mesenchymal stem cell; HIE-hypoxic ischemic encephalopathy; MCAO-middle cerebral artery occlusion