Cell therapy: a new hope for treatment of cerebral palsy ?

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ABSTRACT

Cerebral palsy (CP) is the most frequent neurological disorder associated with perinatal injury of the developing brain. The beneficial impact of stem cells (neural stem cells, mesenchymal stem cells, and embryonic stem cells) is mediated through soluble trophic factors and other cytokines that enable the body to re-establish homeostasis after pathologic and traumatic insults, inflammation, and tissue infarction or degeneration. There is currently no effective therapy for CP. Recently there have been notable advances in the application of cell therapy in neurological disorders. This review provides recent data on the prevention and cell therapy in CP.

Key words: cell therapy, prevention, cerebral palsy

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Received: 27.09.2012
Accepted: 29.11.2012
Progress in Health Sciences
Vol. 2(2) 2012 pp 174-180.

INTRODUCTION

Cerebral palsy (CP) is the most frequent neurological disorder associated with perinatal injury of the developing brain [1]. Major brain lesions associated with CP are associated with white matter damage in preterm infants and cortico-subcortical lesions in term newborns [2]. With the technical progress made in fetal and neonatal intensive care, perinatal mortality has decreased by 25% over the past decade mainly because of the improvements in ventilatory management. Rates of prematurity, however, have increased during the same time period, [3] leading to a higher number of high-risk newborns that suffer from considerable neurological morbidity, often associated with CP [4]. Hypoxic ischemic encephalopathy is a major cause of CP and mortality in infants. Lack of energy causes initially electrical failure and, if it lasts long enough, results in arrest of cellular functions and cell death. Following global ischemia, neurons do not die suddenly or all at once. In some of them, damage develops hours or days after the insult. Most neurons undergo necrosis. In some neurons, hypoxic-ischemic brain triggers apoptosis [5]. Several compounds have been used to interrupt the cascade of neurochemical events triggered by hypoxia- ischemia. Except for hypothermia, which shows satisfactory outcomes only in infants with moderate hypoxic ischemic injury, these therapies have limited results [5].

Furthermore, there is currently no effective therapy for CP. Parents of children with CP often look for new therapies. Stem cells may offer an alternative to the medically proven methods.

Recently there have been notable advances in the application of cell therapy in neurological disorders [6,7]. The mechanisms by which stem cell-based therapies for neurological conditions can lead to functional recovery are uncertain, but structural and functional repair appears to depend on integration of transplanted cell-derived neurons into neuronal circuitries.

Stem cells

The beneficial impact of stem cells (e.g., neural stem cells, mesenchymal stem cells, and embryonic stem cells) is mediated through soluble trophic factors and other cytokines that enable the body to re-establish homeostasis after pathologic and traumatic insults, inflammation, and tissue infarction or degeneration [8,9].

Reports of successful treatments with autologous umbilical cord blood have been published in preclinical studies on animal models of CP, traumatic brain injury, and stroke. Apart from haematopoietic stem cells, autologous umbilical cord blood contains other cell populations, such as mesenchymal stem cells, very small embryonic-like stem cells, unrestricted somatic stem cells, and endothelial precursor cells—all with excellent stem cell capacity and plasticity—characteristics that make autologous umbilical cord blood a strong candidate for future cell-based neurological therapies [6].

Neural stem cells are primordial and uncommitted cells that have been believed to give rise to the vast array of more specialized cells of the central nervous system [10,11]. They differentiate into oligodendroglia and astroglia, and self-renew, migrate, and populate developing and /or degenerating central nervous system regions [12].

Cell transplantation strategies have also received significant attention as an alternative therapy for temporal lobe epilepsy in preclinical studies [12, 13]. Cell therapy may also be useful for decreasing seizures and reversing cognitive and mood dysfunctions when applied after the onset of temporal lobe epilepsy. Neural stem cells are candidates considered for grafting in the domain of cell-based therapy for temporal lobe epilepsy. Neural stem cells can produce trophic factors and the formation of gap junctions [10]. Grafted neural stem cells integrate functionally into the host neural circuitry via early functional gap-junctional coupling, permitting transcellular delivery of homeostasis-modulating molecules as well as directly influencing host network coordinated activity via Ca^{2+} waves.

Mesenchymal stem cells are regarded as excellent candidate for cell therapy because they can be easily isolated, are multipotent, may not require immune suppression, and secrete multiple trophic factors that modulate neurogenesis and apoptosis [14-23].

There is currently a great deal of interest in the use of mesenchymal stem cells to treat neurodegenerative diseases, in particular those that are fatal and difficult to treat, through providing neurotrophic factors to encourage repair and, potentially, new growth of neurons. Proposed regenerative approaches include delivery via intracerebral or intrathecal injection, or even infusion via an intranasal route [24,25]. Mesenchymal stem cells in the brain promote endogenous neuronal growth, decrease apoptosis and regulate inflammation, primarily through the use of secreted factors [24-26].

Neurotrophins

Neurotrophins are a family of closely related proteins (Table 1). They control synaptic function and plasticity and sustain neuronal cell survival, morphology, and differentiation [8,10].

Neurotrophins also regulate cell-fate decisions, axon growth, dendrite growth, and the expression of proteins, such as ion channels, transmitter biosynthetic enzymes, and neuropeptide transmitters that are essential for normal neuronal functioning [14-16].

Classic neurotrophins comprise nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4 [10]. Transforming growth factor-beta 1 has been shown to up- regulate the synthesis of nerve growth factor in cultured rat astrocytes. Other members of this group include neurturin, artemin, and persephin [16]. Transforming growth factor beta plays an important role in tissue regeneration, cell differentiation, embryonic development, and regulation of the immune system. The most prominent feature of glial cell line-derived neurotrophic factor is its ability to support the survival of dopaminergic and motorneurons [17].

The cytokine growth factor family, including a ciliary neurotrophic factor, promotes neurotransmitter synthesis and neurite outgrowth in certain neuronal populations, including astrocytes [18]. Other less-known trophic factors like leukemia inhibitory factor, epidermal growth factor, the neural and thymus-derived activators, the insulin-like growth factors, and the fibroblast growth factor family, consisting of at least 24 different proteins, influence neural development and synaptic plasticity.

However, these are difficult to administer clinically because they do not pass through the blood-brain barrier. It has been demonstrated that there are both neuroprotective and neuro-regenerative effects when neurotrophins are administered either into the cerebral ventricles or directly into the brain [14-16].

This review provides comprehensive data from the last three years of cell therapy in the prevention and therapy of CP in animals and humans.

Method

Search terms

A literature search using PubMed was done for articles in English language from 2010 to July 2012, using the key terms, ‘cerebral palsy’, ‘spastic diplegia’, ‘spastic tetraplegia’, and ‘spastic hemiplegia’, ‘children’ , ‘cell therapy’, ‘stem cells’, ‘mesenchymal stem cell’, ‘neuronal stem cell’, autologous bone marrow-derived mononuclear cells’, ‘human umbilical tissue-derived cells’.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) experimental studies from the last three years of cell therapy in the prevention and therapy of CP in animals; (2) clinical reports from the last three years of cell therapy in the prevention and therapy in children with CP; (3) controlled clinical studies with stem cells in children with CP. Papers were excluded if the aim of cell therapy was other disorders than CP.

RESULTS

Animal experiments

Cell therapy is considered to hold promise for the repair of brain damage. Mesenchymal stem cell transplantation shows therapeutic potential to regenerate the brain cells an ischemic event [24]. Results of the study [24] by Chen and colleagues demonstrated that animals receiving mesenchymal stem cell transplants showed significantly increased antimyelin immune-reactivity in the corpus callosum and improved reaching and retrieval skills compared to animals receiving conditioned medium only. Mesenchymal stem cell transplantation led to significantly more forebrain cell proliferation than in controls.

In another study, Van Velthoven et al. [25] found that a single mesenchymal stem cell treatment at 3 days after neonatal hypoxia-ischemia showed improved sensorimotor function and reduced lesion size in postnatal day 9 mice. Moreover, the same authors demonstrated that intranasal mesenchymal stem cell treatment significantly improved sensorimotor performance in mice after hypoxia-ischemia [26]. Furthermore, mesenchymal stem cell treatment is suggested in the treatment of neurodegenerative diseases, in particular for those that are fatal and difficult to treat, such as Huntington's disease and amyotrophic lateral sclerosis [27].

More recently, Titomanlio and co-researchers [28] showed that neurosphere-derived precursors implanted into the injured brains of 5-day-old pups migrated to the lesion site, remained undifferentiated at day 10, and differentiated into oligodendrocyte and neurons at day 42. Although grafted cells finally died there a few weeks later, this procedure triggered a reduction in lesion size and an improvement in memory performance compared with untreated animals, both 2 and 5 weeks after treatment. The effectiveness of intravenous administration of human umbilical tissue-derived cells was tested in a rodent middle-cerebral artery stroke model after days 1, 7, 30, and 90 [29]. At doses $\geq 3\times10^6$, histological evaluations confirmed enhanced synaptogenesis, vessel density, and reduced apoptosis in the ischemic boundary zone, and increased proliferation of progenitor cells in the subventricular zone of human umbilical tissue-derived cell-treated animals compared to controls. In contrast, Dalous and colleagues [30]

demonstrated that human umbilical cord blood mononuclear cells could not integrate into the developing brain or promote subsequent repair in animals. Furthermore, they found that the intraperitoneal injection of these cells aggravated white matter damage and was associated with systemic inflammation.

Table 1. Role of neurotrophins role in the nervous system

Neurotrophins	**Role**	**Citations**
Nerve growth factor (NGF)	Growth, maintenance, survival of neurons, suppresses inflammation.	Fiore et al. (2009)
Brain-derived neurotrophic factor (BDNF)	Survival of neurons, encourage the growth and differentiation of new neurons and synapses, long-term memory	Skaper (2012)
Neurotrophin-3	Stimulation and control of neurogenesis	Skaper (2012).
Neurotrophin-4	Long-term memory, regulation of appetite and body weight	Fiore et al. (2009)
Transforming growth factor beta (TGF beta)	Tissue regeneration, cell differentiation, regulation of the immune system.	Yoong et al. (2009)
Glial cell-derived neurotrophic factor (GDNF)	Promotes the survival and differentiation of dopaminergic neurons, prevention apoptosis of motor neurons induced by axotomy	de Boer et al. (2012)
Ciliary neurotrophic factor (CNTF)	Promotes neurotransmitter synthesis and neurite outgrowth in neuronal populations including astrocytes.	Wiese et al. (2012)
The epidermal growth factors (EGFs)	Activate synaptic plasticity, neuronal survival and proliferation of glial/stem cells.	Oyagi et al. (2011)
Neuregulins (NRGs)	Promote neuronal migration and differentiation, regulate the selective expression of neurotransmitter receptors in neurons and at the neuromuscular junction. They also regulate glial proliferation, survival and differentiation.	Buonanno and Fischbach (2001)
The insulin-like growth factors (IGFs)	Regulate neural development including neurogenesis, myelination, synaptogenesis, and dendritic branching and neuroprotection after neuronal damage.	Maya-Vetencourt et al. (2012)
Fibroblast growth factors (FGFs)	Play important roles in neurogenesis, axon growth, differentiation and neuronal survival. Activate synaptic plasticity.	Eswarakumar et al. (2005)

Zheng and colleagues [31] studied the neuroprotective effect of vascular endothelial growth factor and neural stem cells in newborn rats with CP. The neural stem cells and vascular endothelial growth factor were administered in the left sensory-motor cortex 3 days after CP model was established. Transplantation of neural stem cells not only resulted in increases in vascular endothelial growth factor protein expression in rat brains, but also largely prevented the behavioral defects and brain tissue pathology.

Case studies

Bone marrow mesenchymal stem cells were administered intravenously four times to an 11-year-old boy with CP [32]. After discharge, the patient could walk more smoothly than before transplantation; in addition, his vision had improved significantly six months after trans-plantation, which was also supported by electrophysiological examination.

Papadopoulos and co-workers [33] assessed the safety and feasibility of autologous umbilical cord blood transfusion with low dose granulocyte colony stimulating factor injections in improving the functional outcome of two children with CP (spastic diplegia). Moreover, granulocyte colony stimulating factor has recently been shown to be a neuronal ligand counteracting programmed cell death and driving neurogenesis [34]. These patients had also physical therapy. Gross Motor

Function Classification System improvements were seen in both patients. They were reclassified as Gross Motor Function Classification System level I, up from level III after two month of the treatment. No side effects have been noted. The mechanism by which human umbilical cord blood stem cells may induce neuroprotection and neurogenesis may involve antioxidant(s) and neurotrophic factors [35].

More recently, Luan and colleagues [36] explored the safety and efficacy of using neural progenitor cells to treat 45 children with severe CP. They performed neural progenitor cell transplantation in the patients by injecting these cells derived from aborted fetal tissue into the lateral ventricle. Motor development was significantly accelerated within the first month after cell transplantation, but the rate of improvement gradually slowed to preoperative levels. After one year, the developmental level in each functional sphere (gross motor, fine motor, and cognition) of the treatment group was significantly higher compared to the control group. No complications have been reported.

In another study, Sharma et al. [37] administered autologous bone marrow-derived mononuclear cells intrathecally and intramuscularly in 71 children suffering from such incurable neurological disorders as muscular dystrophy, CP, autism, Rett syndrome, and giant axonal neuropathy. Fifteen months post-infusion assessment confirmed subjective and functional improvement in 97% of patients with muscular dystrophy. Similar results were noted in patients with spinal cord injury, CP, and other disorders.

Clinical trials

Currently, no controlled study of injections with stem cells in children with CP has been published. At present, five clinical trials on stem cells in patients with CP are registered at ClinicalTrials.gov. [38].

Two of these trials are based in the US and use autologous banked umbilical cord blood. Both studies are double-blind and cross-over, and include patients with CP. The first study assesses the safety and efficacy of autologous cord blood infusion in children with CP, aged 1-12 years, with repeated follow-up over one year with clinical and laboratory evaluations.

The second study evaluates the side effects of bone marrow derived from CD133 in patients with CP aged 4-12 years. Allergic reactions, local infection, meningitis, and encephalitis due to cell transplantation during the first month are assessed. Paralysis or sensory loss below the level of the injection site are evaluated. Speech and motor function are assessed for six months.

A third trial is ongoing in Iran and uses intrathecal autologous stem cells in patients with hypoxic/ischemic brain injury, aged between one month and 18 years. It has been suggested that after introducing hematopoietic cells in the subarachnoid space of the spinal cord, these cells may be transported through the cerebrospinal fluid and can more efficiently deliver to the injured area, as compared to the intravenous route.

A fourth trial was conducted in South Korea and completed in April 2011. Researchers used allogenic umbilical cord blood in combination with erythropoietin in children with CP, aged 10 months to 10 years. It is suggested that erythropoietin is useful in repairing neurological injuries in the brain. The main mechanism of erythropoietin is supposed to be neuroprotection and neurogenesis, which would reinforce the effects of stem cells as well.

In Mexico, the fifth registered clinical trial is currently recruiting participants. This trial uses autologous bone marrow as a stem cell source subsequent to intensive (granulocyte colony stimulating factor) stimulation. The purpose of this study is to determine whether or not the plasticity of autologous intravenous application of cord blood stem cells would improve the clinical course of asphyxiated newborns. Application of autologous stem cells within the first 48 hours after birth will be performed.

CONCLUSIONS

Children with CP have a remarkable ability to recover from early brain injuries (brain plasticity). The focus of rehabilitation treatment has recently shifted to neurological rehabilitation in response to increasing evidence for neuroplasticity [39, 40].

Cell therapy in patients with CP can perhaps offer an additional method of stimulation brain plasticity. At present it is too early to recommend stem cell therapy in those children.

Although many types of stem cells have been proposed in the treatment of CP and neurological disorders, further controlled trials are needed to confirm their efficacy and safety.

Conflicts of interest

The authors have declared no conflicts of interest.

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