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Update on stem cell therapy for cerebral palsy

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Introduction: Due to the publicity about stem cell transplantation for the treatment of cerebral palsy, many families seek information on treatment, and many travel overseas for cell transplantation. Even so, there is little scientific confirmation of benefit, and therefore existing knowledge in the field must be summarized.

Areas covered: This paper addresses the clinical protocols examining the problem, types of stem cells available for transplant, experimental models used to test the benefit of the cells, possible mechanisms of action, potential complications of cell treatment and what is needed in the field to help accelerate cell-based therapies.

Expert opinion: While stem cells may be beneficial in acute injuries of the CNS the biology of stem cells is not well enough understood in chronic injuries or disorders such as cerebral palsy. More work is required at the basic level of stem cell biology, in the development of animal models, and finally in well-conceived clinical trials.

Keywords: animal models, cerebral palsy, embryonic stem cells, induced pluripotent stem cells, mesenchymal cells, multipotent adult progenitor cells, stem cells, transplantation

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1. Introduction

Cerebral palsy is a heterogeneous group of conditions, defined as non-progressive motor disability due to an abnormality of the cerebral hemispheres. While a small proportion of patients with cerebral palsy have as their cause a perinatal hypoxic-ischemic insult, most have acquired cerebral palsy due to the presence of one of a wide variety of other illnesses, such as developmental brain abnormalities, genetic conditions, traumatic or infectious disorders. Furthermore, insults may occur at different times during gestation, resulting in even more variation in pattern and causation. This heterogeneity in cause makes the assessment of any treatment fraught with considerable difficulty.

Parents, on the other hand, focus on the condition of cerebral palsy and seek treatment based on that terminology. Patoine, in a recent editorial [1], described the pressures of a supposed 'miracle cure' supplied by stem cells influencing the behavior of parents of children with cerebral palsy. The United Cerebral Palsy Foundation states that there are 800,000 children and adults in the USA with cerebral palsy. The Centers for Disease Control estimates that about 10,000 babies are born each year with cerebral palsy. Improvements in the care of neonates have done little to alter the percentage of children with cerebral palsy. In fact, the increased survival of very low birth weight infants has contributed to sustaining the present occurrence rate [2]. Thus, the issue of stem cells as a potential treatment for cerebral palsy has assumed a disproportionately elevated position among parents of children with cerebral palsy. Seven years ago we presented in this journal the state of stem cell research in cerebral palsy [3]. While there has been definite progress in the scientific study of multiple types of stem cells, particularly the discovery of induced pluripotent stem cells (iPS cells),

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Article highlights.

- Treatment with stem cells is a serious consideration for cerebral palsy parents.
- Several clinical trials are in progress.
- There are numerous types of stem cells that could be used.
- While there are many animal models of brain injury, none are completely satisfactory for cerebral palsy.
- The potential mechanism of action of stem cells is potentially multifaceted.
- Risks of stem cell transplantation are real and probably understated.
- What is needed includes more knowledge of stem cell biology, a better chronic injury model and, later on, well-conceived clinical trials.

This box summarizes key points contained in the article.

relevant animal models for cerebral palsy are still lacking in critical factors. Consequently, progress with the initiation of cell based clinical trials for treatment of cerebral palsy has been limited.

An additional problem is the timing of treatment. In order to be effective for most patients with cerebral palsy, the treatment will need to address an established or longstanding brain abnormality. But as we accumulate more information about the potential mechanisms of action of stem cells in brain injury, we are led to the conclusion that stem cells are much more likely to be effective in the acute situation rather than long into the course of a chronic disability. However, it is possible that stem cells could act favorably in a chronic injury by replacing nerve cells, with even a small replacement being significant, by making existing connections more effective, or by promoting blood vessel regeneration.

The purpose of this article is to present the current state of stem cell transplantation for cerebral palsy patients. We review the current efforts with patients, the types of cells that might be used, the experimental basis for the treatment, animal models for cerebral palsy, the possible mechanisms for therapeutic success, the need for additional work, and the potential for harm.

2. Stem cell trials for cerebral palsy

There are two ongoing US trials (Duke University and the Medical College of Georgia) listed in ClinicalTrials.gov [4] testing the safety and efficacy of autologous umbilical cord blood for cerebral palsy. These trials are obviously dependent upon the fact that some parents chose to preserve their child's umbilical cord blood at the time of birth. The fact that the cells are autologous gives a significant safety margin to the trials, which otherwise might not have been allowed to proceed. Given that the parents have a strong commitment to stem cell therapy and enter the trials only because they know their children will receive the cells, both these trials are double-blinded with a crossover treatment protocol. The crossover allows the children to receive their cells at some point in the study. The trials attempt to pare down the long list of causes for cerebral palsy by having extensive exclusion criteria, such as athetoid cerebral palsy, autism, hypsarrthymia, intractable epilepsy, progressive neurological disorder, HIV infection, extreme microcephaly, known genetic disorder, obstructive hydrocephalus, significant defect of brain development, chromosomal disorder, presence of major congenital anomaly or severe intrauterine growth retardation. One of the main justifications for these trials is the need to investigate the efficacy of this treatment in the face of ongoing clinical usage of the treatment. Currently there are no US trials for cerebral palsy dealing with allogeneic cell therapies.

While hypoxic–ischemic injury is a clear cut and easily definable cause of cerebral palsy and possibly the most potentially open to treatment, this cohort of patients is in the minority. The current US trials attempt to focus on this group. Perhaps fewer than 100,000 of the 800,000 individuals with cerebral palsy have hypoxic–ischemic injury as their cause.

A third trial listed in ClinicalTrails.gov [4] is being conducted by the Sung Kwang Medical Foundation in the Republic of Korea. This study is double-blinded, randomized with placebo control using allogeneic umbilical cord blood in combination with erythropoietin. The three arms of the study are: i) umbilical cord blood, erythropoietin, and rehabilitation, ii) erythropoietin and rehabilitation, and iii) rehabilitation only. This study employs immunosuppression in order to allow for the use of allogeneic cells.

A fourth trial listed in ClinicalTrials.gov [4] is active but not recruiting (Hospital Universitario, Monterrey, Mexico). In this trial the patients are given G-CSF in order to stimulate their bone marrow to produce stem cells, bone marrow is harvested, and CD 34^+ cells are purified and delivered via the intrathecal route.

Outside the USA, there are a number of facilities that offer treatment with various types of stem cell preparations for cerebral palsy. These facilities are not conducting formal clinical trials. Stem cells offered from these companies or institutions are usually autologous adult stem cells prepared from the patient's own tissue, usually bone marrow. The specific details of the preparation methods are generally not available. The cells are delivered either intravenously or into the cerebrospinal fluid. Often multiple administrations are recommended.

3. Potential cell sources

There are many potential cell sources that have been used for experimental treatment protocols in animal models. The studies employ either direct implantation into brain parenchyma or, more commonly, intravenous injection. We recently reviewed the various cell sources [5].

3.1 Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are bone marrow stromal cells, comprised of a mixture of cell types, capable of supporting hematopoiesis along with the capability to differentiate into multiple cell types. While bone marrow is considered the primary source of MSCs, they are also found in human umbilical cord blood and to a lesser degree in other tissues. MSCs are generally isolated based on their preferential attachment to tissue culture plastic. The cells are fibroblast-like and possess the ability for self renewal. Most of the adult stem cells currently studied share some similarities with MSCs.

In all pre-clinical cerebral palsy studies to date testing MSCs, the cells have been administered in the short term [6-9], with the longest period being one month after injury [10]. The benefit is noted both with intravenous and intracerebral transplantation. The mechanism of cell action is unknown, but does not appear to be neuronal cell replacement. However, the treatment appears to lead to sparing of intrinsic cells. In a primate model, Li *et al.* [11] reported that the cell transplantation resulted in upregulation of IL-10 expression. In association they found a decrease in neuronal apoptosis and astroglial activity in the peri-ischemic area. The number of proliferating cells in the subventricular zone was also increased.

3.2 CD34 cells

CD34 cells are found in umbilical cord blood and bone marrow. They represent a small subset of MSCs. These cells are isolated based on the presence of a transmembrane glycoprotein as their surface characteristic. Clinical trials are underway in stroke patients [4].

3.3 Umbilical cord blood

Umbilical cord blood (UCB) is currently a popular source of adult stem cells being tested as a therapy for disease and injury. Numerous private and public banks have arisen in the USA and other parts of the world. The collection of umbilical cord blood is somewhat controversial in that various organizations, including the American Academy of Pediatrics [12], have questioned the utility of the collection and preservation in private banks. These concerns are based on the contention that there are few, if any, proven autologous therapies. To date, the main usage of these cells has been treatment of childhood diseases of the blood, although their experimental use for the treatment of cerebral palsy is currently under investigation. The minimum necessary dosage of cells for cell engraftment is usually considered to be 1×10^7 cells per kilogram. This includes the total nucleated cell fraction and not just stem cells. Thus, the child will 'outgrow' the available dose of autologous cells obtained at birth and available for transplant at a later date. Should autologous UCB be found efficacious for the treatment of acquired disorders, however, its usage would become wide spread.

UCB has been used experimentally in brain injury models. Benefit of the treatment has been shown in a neonatal hypoxic–ischemic rat model [13], adult rat stroke models [14-16], and a rat traumatic brain injury model [17]. On the other hand, Makinen *et al.* [18] did not find benefit with UCB in a rat stroke model. These were all acute studies.

3.4 Multipotent adult progenitor cells

Multipotent adult progenitor cells (MAPC) (Athersys) are derived from bone marrow as well as other tissue sources [19,20]. The phenotype consists of $CD13^+$, fetal liver kinase 1 $(Flk1)^{dim}$, c-kit^-, $CD44^-$, $CD45^-$, MHC class I^- and MHC class II^-. These cells differentiate into mesenchymal cells, but also cells with visceral mesoderm, neuroectoderm and endoderm characteristics *in vitro*. They proliferate without senescence or loss of differentiation potential. We have used these cells in a rat model of neonatal hypoxic–ischemic injury, where cell administration results in improvement in behavioral outcome and neuronal sparing as determined by histology. We observed benefit in an acute model via both intracerebral and intravenous transplantation routes [21]. This was an important experiment in that we were able to show the efficacy of a safe and practical method of administration, that is intravenous. While some of the transplanted cells survived, and even displayed neuronal markers, the chief restorative feature was enhanced survival of endogenous neurons. We speculated this process was mediated by trophic factors, which would be most efficacious in the acute situation and perhaps less so in a chronic injury, as would be the case for cerebral palsy.

Mays *et al.* [22] reported recent data from our group in a rat model of ischemic stroke. We demonstrated that immunosuppression was not required for allogeneic or xenogeneic cell mediated benefit. The studies noted that improvement with MAPC administration persisted at least as long as six months following acute treatment. Based on histological data, it was concluded that MAPC do not exert their benefit via cell replacement but more probably acted by trophic mechanisms. All of our work with MAPC is in acute studies, and once again we need to show improvement in a chronic injury model in order to supply pre-clinical evidence that would apply to cerebral palsy.

3.5 Induced pluripotent stem cells (IPS cells)

Induced pluripotent stem cells (iPS cells) are now considered to be a substitute for embryonic stem cells [23]. The use of iPS cells has not yet been reported in any preclinical model of brain injury. It seems that the cells may be an ideal source for tissue repair, as they can be prepared from the patient's own fibroblasts, eliminating considerations of rejection. However, there are a number of hurdles that will need to be cleared before this cell type would be available for clinical usage. First, the safety of the cells will need to be amply demonstrated in animal models. Do the cells form tumors? Are the viral agents used in the preparation of the cells a danger to the recipient? Are the cells effective in animal models? Robbins *et al.* [24] reviewed the use of these cells for transplantation and

concluded that reprogramming efficiency and safety considerations would need to be addressed before the initiation of clinical trials. Thus, while iPS cells seem quite promising, much work remains to be done at the basic translational science level before they can move into the clinic.

3.6 Oligodendrocyte progenitor cells

Oligodendrocyte progenitor cells (OPC) may be derived from fetal brain tissue [25], embryonic stem cells or iPS cells, the latter two via cell-differentiation protocols. Once again the problem in relation to the chronic nature of cerebral palsy is that the models of injury utilized in experimental animals are acute. OPC derived from human embryonic stem cells demonstrated some amelioration of function in rats undergoing traumatic spinal cord injury [26,27]. Keirstead *et al.* [28] used human embryonic-stem-cell-derived OPC in a rat model of spinal cord injury and compared the cells in an acute model versus a chronic model. Animals receiving the transplant seven days after the injury showed remyelination and improved motor ability compared with untreated animals; however the animals treated 10 months after the injury demonstrated no statistically significant improvement over control animals. This study underlines the potential difficulty of developing effective therapeutics in the chronic injury setting of the CNS.

Tokumoto *et al.* [29] evaluated the ability of iPS cells derived from mouse embryonic fibroblasts to differentiate into oligodendrocytes and compared this with the differential ability of mouse embryonic stem cells (ESC). They found that intracellular factors inhibited the differentiation of iPS cells into mature oliogodendrocytes.

3.7 Embryonic stem cells

Embryonic stem cells (ESC) are certainly the most controversial type of stem cells. They are derived from embryos and generally require the destruction of that embryo. Consequently, there remain abiding ethical concerns about their use. In addition, the proliferative capacity of the cells and their potential for differentiation into many cell types makes the possibility of tumor formation quite real. Given that children receiving the cells would have many years in front of them, there would be ample time for tumor formation to occur.

The animal models examined with ESCs are all in acute injuries. Zhang *et al.* [30] studied transplantation in a rat stroke model 24 h after the injury and found favorable post-implantation histological changes with survival of the transplanted cells, their migration and differentiation toward neural cell types. Liu *et al.* [31] reported that mesenchymal cells derived from ESCs lessened rat infarction volume, differentiated into neuronal and endothelial cells, and improved functional outcome when injected intravenously. Ma *et al.* [32] showed that embryonic-derived stem cells possessed the ability to migrate into the injury site and improve learning ability and memory fully eight months after the injury. Even though the benefit of the ESCs was long-lasting, the treatment was delivered in the acute phase after injury.

3.8 Fetal stem cells

Finally, stem cells can be collected from fetal tissue. While the utility of these cells has not been widely explored in injury models, there are indeed indications of their potential. Aftab *et al.* [33] demonstrated that retinal progenitor cells from donor tissue of 16 – 18 weeks gestational age were able to integrate into host retina and express rhodopsin. In other experiments cells from fetal brain transplanted acutely after hemorrhagic stroke displayed neuroprotecting anti-inflammatory capacity [34].

4. Experimental models

While cerebral palsy is caused by a number of conditions of which brain injury is a minor component, the models for cerebral palsy are generally based on some type of brain injury. The ideas for various therapies, therefore, are predicated on the notion that we can reverse the effects of the injury. Even though this may be the case for an acute injury, this theme does not apply to the many children with cerebral palsy whose condition arises from abnormalities of brain development. Our discussion in regard to the models of cerebral palsy is confined to the types of cerebral palsy arising from injury.

Johnston *et al.* [35] have recently reviewed the available animal models and concluded that none are fully adequate.

The Rice-Vannucci model [36] which combines unilateral carotid artery ligation with hypoxia in 7-day-old rat pups has been used for numerous studies on the cause and treatment of brain injury in the neonatal animal. These are studies of acute injury.

The use of lipopolysaccharide as a pretreatment to induce vulnerability to hypoxic–ischemic insult has added the important aspect of prenatal infection to the examination of the problem [37]. Girard *et al.* [38] showed that the combination of lipopolysaccharide exposure and hypoxic–ischemic injury in rats mimicked the motor deficits and neuropathological lesions seen in very premature infants. Their motor deficits were more persistent making this one of the more promising models for chronic injury.

In view of the frequency of cerebral palsy occurring related to prematurity, the importance of white matter injury is an important consideration. Periventricular leukomalacia is the most frequent lesion in these patients. White matter lesions are not well-seen in rodent models, as the rodents have comparatively little white matter. In order to mimic the lesion seen in premature infants, several larger animal models have been developed which demonstrate white matter injury [35].

The perinatal rabbit model of cerebral palsy probably best fits the criterion of an injury producing motor disability. This model is produced by uterine ischemia [39-42] or by intrauterine administration of endotoxin [43]. However, these models do not appear to supply the chronic or long-lasting deficit we believe is required for satisfactory assessment.

Larger animal models, such as the sheep [44] or baboon [45], better reproduce the pathology seen in human infants. The pre-term baboon mimics the white matter neuropathology seen in premature human infants [45]. The expense of these methods, however, appears to be prohibitive for the number of animals required for an adequately powered study.

One of the central problems in the development of stem cell therapies for cerebral palsy is still the lack of satisfactory experimental models. Ideally the model should include impairment of movement as a result of a brain injury. Secondly, the model should be one of chronic rather than acute injury. The more critical of these two factors actually is the need for a chronic or long-lasting injury. There have been numerous experimental treatments of acute injury models that have demonstrated success but none that have shown efficacy in a true, chronic model of injury. We and other investigators have shown that acute injuries are subject to repair by cell therapy, while the problem of chronic injury has been more resistant or neglected. The important feature that needs to be demonstrated is the capacity of the cell therapy to repair a chronic injury of any type. The type or location of the brain injury is comparatively less important than the need for a persistent, abnormal behavioral syndrome of some type in the animal.

5. Possible mechanisms of action

One of the main ideas inherent in stem cell transplantation for cerebral palsy is that the stem cells would replace the cells of the damaged nervous system. Most reports dealing with adult stem cells show only a minimal survival of the transplanted cells with few, if any, of these cells displaying markers/functionality of nervous tissue [21,46,47]. It does not appear that replacement alone would be sufficient to account for improvement in the experimental situation. While embryonic or iPS cells may have somewhat greater potential for such replacement and transformation, the number of cells undergoing this process is quite limited *in vivo*. Even though there may be some replacement by transplanted cells, the cells often do not develop normal processes and may not function in neuronal circuitry [48]. Thus, cell replacement as an explanation for any improvement in the models is unlikely to be the case given the current state of our knowledge of the cell biology of stem cells.

Another possibility is that the transplanted cells differentiate into astrocytes [48] or microglia. How this would assist in functional recovery is unclear.

Bone-marrow-derived cells may participate in blood vessel regeneration by promoting adhesion of CXCR4-positive cells onto vascular endothelium [49], recruitment of endothelial progenitor cells [50], and in the formation of periendothelial vascular cells [51]. Borlongan *et al.* [52] have demonstrated that crude bone marrow may form endothelial cells in an animal model of stroke.

A fourth set of ideas related to benefit is that the transplants induce a greater survival of intrinsic cells. We reported this phenomenon in our neonatal hypoxic-ischemic model in animals treated with MAPC [21]. Mahmood *et al.* [53] used MSC injection to demonstrate that transplanted cells increased the expression of nerve growth factor and brain-derived neurotrophic factor after traumatic injury. This idea, for which the evidence seems strong, tends to restrict the benefit of stem cell transplantation to the acute post-injury period.

Another possible mechanism of benefit is the effect of adult stem cells on splenic function during acute brain injury. In a stroke model Vendrame *et al.* showed that UCB lessened the splenic release of inflammatory cells and thereby protected the brain [54]. In support of this concept Walker *et al.* [55] demonstrated that the intravenous injection of MAPC after trauma blocked the normal splenic response to injury and improved outcome. These reports supported the idea that the spleen plays a role in adversely increasing the blood–brain barrier permeability and that the splenic response is blocked by adult stem cell therapy. Once again, this is a benefit only for the acute situation.

6. Risks of treatment

The risks of stem cell therapy occur primarily with allogeneic transplants, which expose the recipient to graft-versus-host disease. Most reports of complications are in children undergoing hematopoietic stem cell transplantation for malignancies. These complications may relate in part to the fact that these children received radiation therapy, chemotherapy, or immunosuppressive medications in addition to the stem cell transplant. Herpes or cytomegalovirus infections may occur in these patients [56]. A variety of other medical complications are also reported in similar groups of patients [57,58]. Woodward *et al.* [59] reviewed 405 patients who received hematopoietic stem cell transplantation for a variety of disorders. Of these patients, 26 experienced some type of encephalopathy due to infection, organ failure, medication reaction, seizures, acute disseminated encephalomyelitis, thrombotic thrombocytopenic purpura or stroke.

Herpes virus-6 encephalitis is also reported as a complication of unrelated umbilical cord transplant [60].

Clearly, we should not consider stem cell transplantation, particularly allogeneic, to be a benign procedure. Autologous transplantation may incur some of the same risks, particularly as the patients may be exposed to chemotherapy or infectious agents. The complications may relate significantly to the treatment accompanying transplantation or the site to which the transplant is delivered, such as into the cerebrospinal fluid.

While adult stem cell transplants have been carried out in large numbers of cerebral palsy patients outside the US, there is no systematic reporting of complications. One would think that the route of administration, that is intravenous versus directly into the CNS, might be a key to the understanding of complications, but the reporting of routes and their complications are unavailable. Without question, the long-term complications are simply unknown.

7. What's needed next

We must have more knowledge of the biology and laboratory manipulation of the different types of stem cells. This area must include more work in the area of cell differentiation strategies. In addition we need to learn more about the effects of the various methods of stimulating intrinsic neural proliferation.

A chronic, pre-clinical animal model is required for the study of the various competing cells types. The different cell types need to be compared in head-to-head competition.

Controlled clinical trials are needed. These should be conducted with very specifically described patient groups, particularly more so than the current, on-going American trials. We must recognize that there are considerable differences among cerebral palsy patients, and therefore the patients need to be carefully matched for each study. This type of trial could only be achieved in a coordinated multiple-center paradigm.

8. Conclusion

Current clinical trials in the use of stem cells for cerebral palsy are ongoing and incomplete. While there are a number of different cell types that are potential candidates as treatments, none have been shown to be effective in chronic animal models. Furthermore, available animal models do not adequately mimic cerebral palsy. Risks of the treatment are reported. More work on understanding the underlying beneficial biology of stem cells and the development and validation of more relevant animal models is required.

9. Expert opinion

Stem cell therapy for cerebral palsy remains a frustrating area. Considering all the publicity about stem cells and the fact that cell therapy is widely available outside the USA for a price, parents feel that surely the treatment must work. This view tends to be confirmed by preclinical reports of benefit in animal models of acute injury. Anecdotal reports of success, of which there are many, contribute little toward clarifying any benefit, but nevertheless encourage parents of cerebral palsy patients to seek the unproven therapy. There is no evidence as yet that stem cell therapy works in a chronic model of injury, as would be relevant to cerebral palsy.

The problem remains difficult for several reasons: cerebral palsy is not a homogeneous disease, our knowledge of stem cell biology is in its infancy, the pre-clinical models are far from ideal, and various preclinical trials show efficacy in acute models leading to falsely raised hopes.

We need a safe cell type that is effective in a chronic animal model of brain injury. Despite clinical use of stem cell treatment for cerebral palsy in many sites outside the USA, evidence of efficacy in a chronic animal model will be necessary before a clinical trial will be allowed in the USA using any type of allogeneic cell. We believe it would be inappropriate to conduct a clinical trial for cerebral palsy using allogeneic cells without safety and efficacy data in a chronic animal model.

For the time being it may better to focus on the treatment of acute brain injuries with stem cells and thereby the improvement or prevention of cerebral palsy in this subset of patients.

Declaration of interest

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