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Revision

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Stem cells: an alternative for the treatment of cerebral palsy

Células madres: una nueva alternativa en el manejo de la parálisis cerebral

Keywords

cerebral palsy, stem cells, therapy, GMFCS cerebral palsy, stem cells, therapy, GMFCS

Abstract

Cerebral palsy it's a high impact pathology in general population, generating big costs for the public health system. With an increase of its prevalence resulting in a high incidence rate of premature low weight new born. Presently, there has been in an increasing interest in producing basic and clinical research with the aim on therapeutic value from transplant using pluripotent, particularly in children affect by cerebral palsy. This paper describes a comprehensive review from 13 informative papers that covers the mayor attributes on this newly developed technic.

Palabras clave

parálisis cerebral, células madre, terapéutica, GMFCS, reparación cerebral

Resumen

La Parálisis Cerebral (PC) es una patología de alto impacto en la población general, generando grandes gastos en el sistema de salud. Con un aumento de su incidencia en los últimos años por el nacimiento de prematuros de muy bajo peso. Actualmente se está desarrollando investigación en ciencias tanto básica como clínica con el fin de evaluar el potencial terapéutico de las células madre en la funcionalidad y calidad de vida de niños con PC. En este estudio se revisaron 13 artículos con el fin de evidenciar la seguridad y eficacia de esta terapia, e implementar en el futuro el uso de células madre en el tratamiento de pacientes con PC.

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Introduction

In context with Cerebral Palsy

Cerebral Palsy (CP) affects one in 500 school-age children. In recent years, it has been defined as a non-progressive motor syndrome with clinical manifestations that change with age, causing a limitation of motor activity. Associated with injury or malformation during fetal brain development or in childhood, it affects muscle control, coordination, tone, and reflexes, as well as body movement and balance.[1,2,18] It can also affect fine and gross motor skills, as well as oral motor functioning.[2,18]

CP is caused by brain injury or malformation during the period of brain development in the prenatal or perinatal stage, or immediately after birth.[1-3]

Risk factors and potential etiologies of CP depend on the time of injury (prenatal, perinatal, or postnatal) and on biological, temperamental-psychological, familial, and social factors.[1]

The following risk situations may intervene in the different ages of the child: fetal intrinsic factors such as fetal genetics, infections, and endocrine factors; placental factors such as placental size, structural and functional abnormalities, environmental factors, and infections; and extrinsic factors which may include maternal nutritional status, maternal age, education, multiple gestation, cigarette consumption, alcohol, medications, and history of prematurity.[1]

There are multiple etiologies for CP, so the most important thing is early detection of neurodevelopmental problems. Some of the main issues associated with prematurity are hypoxia and ischemia, intraventricular hemorrhage, and auditory and visual dysfunction. Postnatal problems involve infections, cranioencephalic trauma, cerebrovascular disease, and bronchopulmonary dysplasia.[1]

There are various classifications for CP, including pathophysiological classifications (type of tension: dystonia, chorea, ballism, rigidity, ataxic, and mixed types) and topographic classifications (quadriplegia, diplegia, hemiplegia, and double hemiplegia).[1]

For practical applications of this article, however, it is important to know the gross motor function classification system (GMFCS). This universal classification system evaluates the degree of functionality or limitation of the patient and is divided into five domains:[4]

GMFCS Level I: walks without limitations.

GMFCS Level II: walks with limitations.

GMFCS Level III: walks aided by mobility devices.

GMFCS Level IV: self-mobility with the use of motorized help. Limited self-mobility, wheelchair use probable.

GMFCS Level V: severe limitations in the head and trunk. Requires extensive use of assistive technology and physical assistance; transported in a wheelchair.

The current therapeutic measures are observation, facilitation of neurodevelopment, feeding, sleep, development of skills and manual dexterity, improvement of positions and basic postures of development, general mobility, communication and language, leisure time use, and abilities and attitudes for their development, all of which are implemented through physiotherapy, language therapy, and occupational therapy. The current medical management consists of oral antispastic, baclofen bomb, selective dorsal rhizotomy, benzodiazepine, and botulinum toxin.[1]

In context with Stem Cells

Stem cells are currently of great interest in the area of scientific research. They have great therapeutic potential in multiple hematopoietic, osteoarticular, cardiovascular, and neurological pathologies due to their characteristics of self-renewal, differentiation, and derivation to a mature cell. Stem cells are divided according to their origin in embryonic and adult, and according to

their potential of differentiation into pluripotent, multipotent, and totipotent.[5]

Types of stem cells (SC)

* Bone marrow SC: generate hematopoietic, blood system, and mesenchymal cells.[5]

* Umbilical cord blood, placenta, and Wharton's jelly SC: generate heterogeneous populations with pluripotent potential. [5]

* Neural SC: capable to differentiate into glia and astrocytes.[5]

* Adipose tissue SC: heterogeneous cell population including mesenchymal and endothelial progenitors.[5]

* Skin SC: generate dermis, epidermis and subcutaneous cellular tissue.[5]

Stem cells' restorative potential for the brain in patients with CP

Stem cells have been studied in multiple brain pathologies such as stroke, hypoxic-ischemic encephalopathy, autism, neurodegenerative diseases, and cerebral palsy, due to their great potential for proliferation and tissue restoration.

Several clinical and preclinical studies investigate the brain repair mechanisms as well as the safety and efficacy of stem cell therapy in patients with CP.

Although the exact mechanism of brain tissue repair is still being studied, it is considered that SC influence the repair by means of paracrine and trophic effects such as increased synaptogenesis, stimulation of endogenous mechanisms of repair, stimulation of angiogenesis, neovascularization, cellular migration, and stimulation of the proliferation of endogenous stem cells; these have, in a smaller way, the capacity of proliferation, differentiation, and integration of SC to brain tissue, which results in the replacement of neurons and glia and we thus obtain remyelination, with subsequent increase of neuronal plasticity and improvement in motor function.[6]

Stem Cells and Cerebral Palsy - Animal Models

Brain injury causes motor and cognitive development deficit, which incurs great costs for the healthcare system due to the children's requirements. At present, the incidence of cerebral palsy is eight per 1000 live births. This has grown in recent years due to the increased survival of very low birth weight preterm infants and patients with brain damage secondary to hypoxic-ischemic encephalopathy.[6] In spite of this, the therapeutic strategies used for CP have not shown significant improvements in the functionality or in the repair of the brain, for which the therapeutic potential of SC for the regeneration of brain tissue and subsequent functional rehabilitation has been investigated.6 Different studies in animal models obtained successful results and identified some of the brain repair mechanisms.

In 2006, Meier *et al*. studied 36 rats to evaluate the therapeutic potential of stem cells derived from umbilical cord blood (UCB). Following brain injury due to hypoxic-ischemic encephalopathy caused by ligation of the left carotid artery at seven days of age, they subsequently gave intraperitoneal transplantation of cells derived from human UCB stem cells. The results indicated the presence of human HLA-specific antigens in the lesion area, suggesting cellular migration, and also identified a significant improvement in locomotor functionality (p=0.001) with a significant decrease in spastic paresis (P=0.001). [7] (See table 1.1).

In 2012, Sang-Hun Bae, *et al*. studied 60 rats in which the left carotid artery was ligated with subsequent brain injury. They treated them by intravenous transfusion of UCB-derived stem cells at doses of 1x107 cells. They evaluated human immunoreactivity, 3-phosphate dehydrogenase levels, PCR to identify human RNA, and cytokine measurements. The results showed presence of SC in the ipsilateral and contralateral regions of the lesion suggesting neuroprotection of uninjured tissue, in addition to immunomodulation, neovascularization, increased cell proliferation and microglia.[8] (See table 1.2).

Table 1.1 Animal models.

Authors	Meier C, Middelanis J, Wasielewski B, Neuhoff S, Roth-Haerer A, Gantert M, Dinse HR, Dermietzel R, Jensen A.
Study	Experimental protocol - rats as animal model.
Country/Year	USA / 2006
# Patients	36
Follow-up	24 days
Pathology	Spastic Cerebral Palsy due to Perinatal Hypoxia-Ischemia.
Treatment	1. Group II: Sodium chloride 0.9% 500microL 2, Group III: 107 mononuclear cells derived from umbilical cord blood
Via	Peritoneal.
Results	1. Immunohistochemistry detected surface-specific human HLA-DR antigen chains which demonstrate that transplanted human mononuclear cells migrated from the intraperitoneal cavity to the damaged brain region. 2. Detected within 3 days. 3. The transplanted cells were strictly confined to the area of activated microglia. 4. Transplantation of hUCB cells did not change the severity of the morphological damage. 5. Reduced spastic paresis compared to controls in 3 days. 6. The results suggest an immune degree of tolerance towards cord blood cells, possibly mediated by a decrease in cytotoxic host responses.
References	Meier C, *et al.*[7]

Table 1.2 Animal models.

Authors	Bae SH, Kong TH, Lee HS, Kim KS, Hong KS, Chopp M, Kang MS, Moon J.
Study	Experimental protocol - rats as animal model
Country/Year	USA /2012
Follow-up	Between 1 and 10 weeks.
Pathology	Cerebral Palsy due to Perinatal Hypoxia-Ischemia
Treatment	HUCBCs 1x107/200microL
Via	IV
Results	1. Rats survival 80%. 2. Easy cells penetration to the blood-brain barrier. 3. Presence of HUCBCs around the ventricle ipsilateral to the ischemia . 4. Neuroprotection in mature neurons 10 weeks post (cells against laterals). 5. Increased activity of microglia in the disease stage. 6. Modulation of brain damage (IL8, 6-CSF, mcp-1). 7. Functional improvement 10 weeks after transfusion . 8. Secretion factors of angiogenesis, chemokines and IL. 9. Increase intercellular communication and cellular migration.
References	Bae SH, *et al.*[8]

Table 1.3 Animal models.

Authors	Drobyshevsky A, Cotten CM, Shi Z, Luo K, Jiang R, Derrick M, Tracy ET, Gentry T, Goldberg RN, Kurtzberg J, Tan S.
Study	Experimental protocol - rabbits as animal model.
Country/Year	USA/2015
Follow-up	11 days.
Pathology	Cerebral Palsy secondary to Prenatal Hypoxia-Ischemia.
Treatment	2.5 x 106 HUCB.
Via	IV
Results	1. Initially no difference in deficit control and treatment. 2. First day of treatment improvement in Locomotion, Tone, Posture, Correction. 3. Diminished hypertonia and dystonia. 4. Cell propagation and increased vascularization identified with DNA (PCR) more in cortex and thalamus. 5. HUCBC high doses decrease deficit. 6. There was mortality from IV infusion caused by pulmonary embolism related to rapid infusion.
References	Drobyshevsky A, *et al.*[9]

Table 2.1 Umbilical Cord Blood (UCB) stem cells.

Country/Year	Korea/2013
# Patients	105
Follow-up	3-6 months
Pathology	CP
Treatment	Groups: 1. UCB + rhEPO + Rehabilitation Group pUCB 2. rhEPO + UCB placebo + Rehabilitation Group EPO 3. Rehabilitation + UCB placebo + rhEPO placebo UCB Dosis 3 x 107 Kg
Stimulus	Rehabilitation therapies
Via	IV
Results	*The infusion of allogeneic UCB potentiated with rhEPO showed improved motor and cognitive function in children with CP. * Pneumonia and irritability were the more frequent adverse events. * A death was evidenced related to difficulty in swallowing and possible aspiration. * Superior benefits in the pUCB group in motor and cognitive function. * Remarkable improvement in the period of 3 to 6 months. * Most favorable response in children under 36 months. * Premature babies had better motor results. * Term babies had better cognitive results. * Cyclosporin was used, which could be the cause of some AE.
References	Min K, *et al.*[11]

rhEPO - Recombinant human erythropoietin

A 2015 Duke University study by Drobyshevsky *et al*. was performed on rabbits with prenatal ischemia induced by occlusion of the uterine artery at 22 days of gestation and subsequent reperfusion until birth (31.5 days). This was followed by intravenous transfusion of 5x106 UCB-derived stem cells. When the results were analyzed there was a significant improvement ($p<0.05$) at five days in posture, at five and 11 days in locomotion, and at five and 11 days in tone and dystonia, which was correlated with an increase in cellular concentration. There was significant improvement ($p<0.05$) in all domains at five and 11 days with low doses.[9] (See table 1.3)

Stem Cells and Cerebral Palsy - Clinical Trials

At www.clinicaltrials.gov there are 24 clinical trials of SC treatment in patients with CP, of which the following have shown results:10

Studies with UCB-derived SC

A double-blind, randomized, placebo-controlled study was undertaken in 2013 by Min, *et al*. They studied the therapeutic potential of UCB-derived SC with erythropoietin (rhEPO) and rehabilitation in 105 children with a three to six months follow-up. The results showed that the infusion of allogeneic UCBSCs enhanced with rhEPO achieved a superior response than the placebo groups in terms of motor and cognitive function in children with CP, and the response in patients younger than 36 months was better. Some adverse events were reported, related to the use of cyclosporine. Failure in the group with single transplantation does not allow the conclusion to be drawn as to whether the improvement in functionality was due to SC or the use of cells enhanced with rhEPO.[11] (Table 2.1)

A study conducted in 2014 by Cotten, *et al*. treated 23 patients with hypoxic-ischemic encephalopathy with intravenous transfusion of UCB-derived cell analogs in doses of 1-5 x 107 cells, with a 12-month follow-up. The study did not show any adverse events (there were two deaths unrelated to the therapy, due to the severity of the comorbidities) and resulted in improvement of at least three of the six domains evaluated: 1. Level of consciousness, 2. Spontaneous activity, 3. Tone, 4. Posture, 5. Primitive reflexes, and 6. Autonomous functions.[12] (Table 2.2)

In 2015, the study conducted by Feng, *et al*. evaluated the safety of umbilical cord-derived allogeneic SC therapy in 47 patients with CP. The transplanted doses of 2-3 x 107 were given in four to eight injections, the first intravenous and the remaining intrathecal. The paraclinical evaluation, signs, symptoms, and vital signs measurements resulted in normal pre- and post-infusion paraclinicals (<0.05), with no evidence of adverse events from the initial IV infusion. The intrathecal infusion, however, did report adverse events such as 42.6% fever, 21.2% vomiting, three convulsions, three headaches, two respiratory infections, two incidences of dermatitis, one abdominal pain and constipation. An age of ≤10 years old at onset of treatment was identified as a significant risk factor (=0.036) to develop AE.[13] (Table 2.3)

The study conducted in 2015 at Duke University by Romanov, *et al*. included 80 patients who received intravenous infusion of 3-3.5 x 108 UCBSC and follow-ups from 3 to 36 months. No adverse events were reported. Significant improvement in the tone of the limbs was evident (p=0.0002-0.0004), upper extremity strength (p=0.025), reduction of the epileptic paroxysm, and improvement in the mental sphere (memory, attention, intellectual and emotional development). The results obtained referred to the ability to sit without support (Level IV), walk with support (Level III) or walk without support (Level II). The authors suggest that the therapy was more effective in patients two to six years of age, with a greater number of infusions, and a lesser degree in the severity of the disease.[14] (Table 2.4)

Studies with bone marrow-derived SC

A study conducted in 2013 by Chen, *et al*. evaluated the efficacy of bone marrow-derived stem cell therapy in 60 patients with CP, with GMFCS levels III-V. They were administered an intrathecal dose of 1-2 x 107 bone marrow-derived SC with a six-month follow-up. The results show a significant improvement in the GMFM scale score (P=0.011 and 0.001) at three and six months post-transplant,

Table 2.2 Umbilical Cord Blood (UCB) stem cells.

Country/Year	USA/2014
# Patients	23
Follow-up	12 months
Pathology	Hypoxic-ischemic encephalopathy.
Treatment	1-5 x 107 UCB cells.
Via	IV
Results	* There was no evidence of adverse events from the infusion. * No significant changes in the first two infusions (AF, AT, nor O2SAT). * O2SAT decreased after the third and fourth infusion. * A patient of 35 weeks gestation with cord pH of 6.72 (stop). * A patient with E. coli received ampicillin/cefotaxime for 21 days (stop). * Significant improvement in at least 3 areas. * Two patients died at 14 months. The first, diagnosed with chromosome 17p12 deletion as well as Wolff-Parkinson-White (WPW) syndrome, died due to respiratory syncytial virus pneumo nia. The second with encephalopathy due to severe cystic encephalomalacia, diagnosed with cytomegalovirus infection during his 5th postnatal week, died of acute gastroenteritis with hypovolemic shock.
References	Cotten C M, *et al.*[12]

compared to the baseline and control group. There was no significant language improvement in any of the groups at one month, three months, and six months (p=0.751, 0.522, and 0.304 respectively). No adverse events were reported.[15] (Table 3.1)

Another study was conducted in 2015 by Sharma, *et al*. They evaluated the safety, viability, and efficacy of intrathecal transplantation of autologous stem cells derived from bone marrow in 40 patients with all types of CP with an intrathecal dose of 10.23 x 106 cells and immunosuppression with prednisolone IV, followed up for six months. The evaluation was performed in different domains, in which significant improvement was found in seated balance (p=0.00443), standing balance (p=0.00443), walking balance (p=0.00443), movement of the extremities (p=0.02334) and nonsignificant improvement in upper extremities tone (p=0.13361), lower extremities tone (p=0.073), and trunk muscles tone (p=0.13361) in the diplegia group. In the quadriplegia group, significant improvement was found in all domains (p<0.05) including oral motor functions (p=0.0015), cephalic support (p=0.00443), and cognition (p=0.0015). SPECT performed at the beginning of treatment and at six months post-treatment showed increased metabolism in the frontal, temporal, parietal, basal ganglia, thalamus, and cerebellum areas. No severe adverse events were reported.[16] (See table 3.2)

Studies with embryonic SC

In 2014, a study by Shroff, *et al*. reported on the efficacy of therapy with human embryonic stem cells (hESC) in 101 patients <18 years old with CP. There were four phases in which different doses were used, administered subcutaneously, intravascularly, and intrathecally, in addition to the administration of ophthalmic, oral, and otic drops in children with neurosensorial depression. This study reports significant improvement (p<0.05) in all GMFCS levels: 42 patients started on level V, 21 were on level IV, 15 on level III, 12 on II, and one on I. At the end of the study, no patients remained on levels V or IV, 12 patients got to level III, 50 patients to level II, and 29 patients finished on level I. SPECT also showed improvement in perfusion after receiving hESC therapy. In children with hearing impairment there was improvement in hearing closely. Non-severe adverse events were reported only in the early stages of treatment.[17] (Table 4)

Table 2.3 Umbilical Cord Blood (UCB) stem cells.

Country/Year	China/2015
# Patients	47
Pathology	CP
Treatment	2-3 x 107 UCB cells in 4 to 8 injections.
Via	First infusion IV, rest of infusions intrathecal.
Results	* Normal paraclinical evaluations pre-and post- transfusion. * No AE in initial IV infusion. * Adverse events on intrathecal infusion: Fever 42.6%, Vomiting 21.2%, 3 Seizures, 3 Head aches, 2 Respiratory infections, 2 Dermatitis, 1 Abdominal pain and constipation. All of them improved with symptomatic treatment at 72 hours. * More adverse events in children under 10 years. * Increased motor function. * Less risk of leukemia, tumors, and infections. * Safe Therapy.
References	Feng M, *et al.*[13]

Table 2.4 Umbilical Cord Blood (UCB) stem cells.

Country/Year	Russia/2015
# Patients	80
Follow-up	3 to 36 months
Pathology	CP and related complications.
Treatment	3-3.5 x 108 UCB cells.
Stimulus	Rehabilitation therapies.
Via	IV
Results	* Neurological improvement (diminished muscle and tone pathology, improved tone of the limbs, increased muscle strength, reduced paroxysmal epilepsy). * Improvement in the mental sphere (memory, attention, and intellectual and emotional development). * 23 children showed progress in physical and mental areas. * 17 patients showed no improvement. * 18 patients showed significative progress in motor activities. * No adverse events. * More effective in patients aged 2-6. * Other predictors of the success of the therapy are the amount of infusion of cells and the severity of the disease. * The group of patients who did not respond to the therapy was related to the severity level of their CP and these patients received no more than two doses.
References	Romanov YA, *et al.*[14]

Table 3.1 Bone marrow stem cells.

Country/Year	China/2013
# Patients	60
Follow-up	6 months
Pathology	CP
Treatment	1-2 x 107 stem cells derived from bone marrow.
Stimulus	Rehabilitation therapies.
Via	IV
Results	* 1, 3, 6 months after the transfusion were evaluated. * The two groups increased function in 6 months. * Control group had no significative changes. * Treatment group did show significative changes at 3 and 6 months. * No evidence of adverse events. * No improvement in language.
References	Chen G, *et al.* [15]

Table 3.2 Bone marrow stem cells.

Country/Year	India/2015
# Patients	40
Follow-up	6 months
Pathology	CP
Treatment	10.23 x 106 stem cells derived from bone marrow.
Stimulus	Rehabilitation therapies.
Via	Intrathecal.
Results	* Diplegia group 100% improvement in sitting balance, 90.91% in gait balance, 90% in movement of upper extremities, 83.3% in oromotor activities, 80% in cognition, 70% in movement of lower extremities, 66.6% in language, 50% in ambulation, 45.45% in muscle tone in the lower extremities, 44.44% in lifting activities, 40% in the trunk's muscle tone, 36.36% in muscle tone in the upper limbs. * Quadriplegia group 83.33% showed improvement controlling the neck, 78.95% in sitting balance, 63.16% in cognition, 60% in oromotor skills, 54.55% in ambulation, 52.38% in muscle tone in the lower extremities, 50% in muscle tone in the upper limbs, 45.45% in speech, 45% in the trunk's muscle tone, 36.36% in standing balance, 31.58% in walking balance. * Mixed group 83.33% improvement in speech and foot balance, 66.67% in walking balance, 60% in oromotor skills, 50% in sitting balance and muscle tone in the lower extremities and trunk, 33.33% in muscle tone in the upper extremities. The dystonia patients improved. * 7.5% no improvement. *17.5% minor improvement. *50% moderate improvement. *25% major improvement.
References	Sharma A, et al.[16]

Table 4. Human embryonic stem cells (hesc).

Country/Year	India/2014
# Patients	101
Follow-up	12 months.
Pathology	CP
Treatment	hESC
Stimulus	Rehabilitation therapies.
Via	SC IV Intrathecal, ophthalmic, otic, and oral drops.
Results	* 69% cognitive improvement. * 80.3% recognition/sensitization. * 78.9% aggressiveness. * 74.5% following commands. * 29 patients ended in GMFCS-E&R 1. * 50 patients ended in GMFCS-E&R 2. * 12 patients ended in GMFCS-E&R 3. *No patients ended in GMFCS-E&R 4 and 5. Patients' SPECT showed improvement in perfusion after receiving stem cell therapy.
References	Shroff G, *et al.* [17]

Discussion

Every day, children around the world suffer from prenatal, perinatal, or postnatal brain damage, resulting in death, or in some cases PC, and the main cause is typically hypoxic-ischemic encephalopathy. Improved health care strategies in recent years have helped reduce perinatal mortality, but these survivals have resulted in an elevated CP incidence. Current therapeutic strategies, however, have not achieved significant improvement in motor functions or brain repair.

For approximately 20 years, the therapeutic potential of stem cells has been studied in multiple brain pathologies such as stroke, hypoxic-ischemic encephalopathy, autism, CP, and degenerative diseases.[6] Nevertheless, current clinical trials in CP are limited.

Although the studies about this therapy are in phases I and II of scientific investigation at the moment, we can consider, thanks to some animal models and clinical trials, that the analog or autologous stem cell therapies are a promising alternative for the treatment of children with CP.[6]

Stem cells are a great opportunity in CP because by many paracrine and trophic factors they generate brain repair and, later, functional rehabilitation.6 In animal models, there has been evidence of improved motor function following the transfusion of stem cells derived from umbilical cord by multiple mechanisms - such as cell migration from the site of injection to the lesion site, and even to the contralateral site of the lesion, which is related to a neuroprotective effect. In addition, other effects found in these studies include the evidence of the presence of human stem cells in the animal brain identified through immunohistochemistry of human HLA.

The clinical trials analyzed in this document demonstrate stem cell safety and suggest efficacy in the rehabilitation of children with CP. The mechanisms by which the brain repair is developed are not clear; however, in animal models, we can see changes such as cellular migration, neovascularization, and production of endogenous stem cells with posterior remyelination, which produce an improvement in the motor and cognitive functions. In spite of the significant findings from these studies, there is a lack of data for the exact evaluation of the improvement in the patients studied, such as the specific progress of each CP level according to the GMFCS scale. All studies demonstrate the safety of this therapy as there are no reports of severe post-transfusion adverse events. All investigations have evaluated the patients in a period ranging from three months to a maximum of 36 months, making it difficult to assess the adverse effects and long-term functionality of the individuals studied.

Conclusion

Stem cells have a great potential for brain repair and functional rehabilitation with minimal adverse events; however, more controlled and more specific clinical trials are required to demonstrate the long-term efficacy and safety of patients.

Conflict of interest
There are no conflicts of interest for any of the authors in this scientific report.

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