Concise Review: Stem Cell Interventions for People With Cerebral Palsy: Systematic Review With Meta-Analysis

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ABSTRACT

Evidence for stem cells as a potential intervention for cerebral palsy is emerging. Our objective was to determine the efficacy and safety of stem cells for improving motor and cognitive function of people with cerebral palsy. Searches were conducted in October 2015 in CENTRAL, EMBASE, MEDLINE, and Cochrane Libraries. Randomized controlled trials and controlled clinical trials of stem cells for cerebral palsy were included. Two authors independently decided upon included trials, extracted data, quality, and risk of bias. The primary outcome was gross motor function. Secondary outcomes were cognitive function and adverse events (AEs). Effects were expressed as standardized mean differences (SMD) with 95% confidence intervals (CI), using a random-effects model. Five trials comprising 328 participants met inclusion criteria. Four cell types were studied: olfactory ensheathing, neural, neural progenitors, and allogeneic umbilical cord blood (UCBs). Transplantation procedures differed from central nervous system neurosurgical transplantation to intravenous/arterial infusion. Participants were followed short-term for only 6 months. Evidence of variable quality indicated a small statistically significant intervention effect from stem cells on gross motor skills (SMD 1.27; 95% CI 0.22, 2.33), with UCBs most effective. There were insufficient and heterogeneous data to compare cognitive effects. Serious AEs were rare (n = 4/135 [3%] stem cells; n = 3/139 [2%] controls). Stem cells appeared to induce short-term improvements in motor skills. Different types of stem cell interventions were compared, meaning the data were heterogeneous and are a study limitation. Further randomized controlled trials are warranted, using rigorous methodologies.

SIGNIFICANCE

Stem cells are emerging as a scientifically plausible treatment and possible cure for cerebral palsy, but are not yet proven. The lack of valid animal models has significantly hampered the scope of clinical trials. Despite the state of current treatment evidence, parents remain optimistic about the potential improvements from stem cell intervention and feel compelled to exhaust all therapeutic options, including stem cell tourism. Receiving unproven therapies from unvalidated sources is potentially dangerous. Thus it is essential that researchers and clinicians stay up to date. A systematic review and meta-analysis summarizing and aggregating current research data may provide more conclusive evidence to inform treatment decision making and help direct future research.

INTRODUCTION

Cerebral palsy (CP) is the most common physical disability in childhood, with an incidence of 2.1 per 1,000 live births [1]. CP is a lifelong condition, and disability increases with age [2]. Care, loss of income, and tax revenue losses from cerebral palsy cost the Australian and American economies $87 billion per annum [2]. For the first time in history, the rate of CP in the developed world is beginning to decline [3]. Despite this pleasing progress in the prevention of CP, for those individuals with CP it remains an incurable condition.

By definition, individuals with cerebral palsy have motor impairments that can be grouped into five levels of severity, from ambulatory to wheelchair dependent, using the Gross Motor Function Classification System (GMFCS) [4]. However, almost all individuals experience additional comorbidities, often leading to additional impairment [5]. For example, among people with cerebral palsy, 3 in 4 are in pain, 1 in 2 have an intellectual disability, 1 in 3 cannot walk, 1 in 3 have a hip displacement, 1 in 4 cannot talk, 1 in 4 have epilepsy, 1 in 4 have a behavior disorder, 1 in 4 have bladder control problems, 1 in 5 have a sleep disorder, 1 in 5 are blind, 1 in 15 are tube fed, and 1 in 25 are deaf [6].
Description of the Intervention

Numerous rehabilitative and medical interventions exist that help people with cerebral palsy to both develop functional skills in spite of their permanent physical disability and prevent further physical deterioration from secondary impairments [7]. Despite evidence for the efficacy of rehabilitation and surgical interventions for the treatment of comorbidities in people with CP, no single medical or rehabilitation treatment currently exists that cures the condition, reduces the severity of the condition, or helps the individual progress upward into a milder GMFCS level. Understandably, people with cerebral palsy and their families are strong advocates for urgent research into treatments targeting cure [8]. One of their highest-priority research topics (that they identify) is the efficacy of stem cells for promoting brain repair [8].

Eminent stem cell scientists and cerebral palsy experts unanimously advised the California Institute for Regenerative Medicine that there was sufficient scientific evidence that “cell replacement therapies might be particularly effective for cerebral palsy” [9]. First, because the brain damage in cerebral palsy is often “regionally restricted, non-progressive, and appears limited to a few cell types, [thus] stem cell therapy has tremendous potential” [9]. Second, because cerebral palsy involves demyelination either through primary oligodendrocyte injury or through secondary Wallerian degeneration, processes common to other diagnoses already pioneering stem cell research, “Cell replacement therapies are exciting eventual options for treating cerebral palsy, and cerebral palsy could be a good testing ground for stem cell replacement in the brain” [9].

The following types of stem cells have been identified for potential use in cerebral palsy: amnion epithelial cells (hAECs), CD34-expressing cells from umbilical cord blood, embryonic stem (ES) cells, fetal stem cells, induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), multipotent adult progenitor cells (MAPCs), neural stem cells (NSCs), olfactory ensheathing cells, oligodendrocyte progenitor cells (OPCs), and umbilical cord blood (UCB)/human UCB [10–12].

How the Intervention Might Work

The mechanisms by which stem cells might treat cerebral palsy are proposed to include (a) regenerative mechanisms, replacement and/or repair of damaged brain cells brought about by engraftment and proliferation of transplanted cells, which may or may not include differentiation of transplanted cells into new microglia or astrocytes to promote reorganization; (b) anti-inflammatory mechanisms, attenuation of the inflammatory immune response to brain injury, via a reduction in the release of excitotoxins, cytotoxins, and oxygen free radicals, which if used early enough might evoke a protective response that reduces the size and extent of the white matter injury; and (c) trophic mechanisms, to promote cell survival via release of neurotrophic factors secreted from progenitor cells to induce endogenous cell migration, proliferation, and differentiation and/or to promote angiogenesis and new blood vessel formation [10–12].

Why It Is Important to Do This Review

Stem cells are emerging as a scientifically plausible treatment and possible cure for cerebral palsy, but are not yet proven. The lack of a valid animal model for such a heterogeneous condition has significantly hampered the translation of laboratory-based research and, in so doing, has limited the scope of patient-based clinical trials [10].

Despite the state of current treatment evidence, parents remain optimistic about the potential improvements from stem cell intervention [13] and many parents are compelled to exhaust all therapeutic options for their child [14], including stem cell tourism [13]. Stem cell tourism clinics could be viewed as exploiting desperate families who have exhausted established medicine and rehabilitation interventions and find the wait for stem cells to progress to clinical trials and established therapy too slow [15]. The safety and efficacy of stem cell treatment and tourism are not yet clear and apart from the great costs to the family, there have been several anecdotal reports of serious side effects, including death [16]. Despite this, such clinics often make claims regarding the benefits of treatment, without risks disclosed or ongoing safety monitoring [15]. Receiving unproven therapies from unvalidated sources [15] is potentially dangerous. Thus it is essential that researchers and clinicians stay up to date with the outcomes from the numerous registered stem cell clinical trials that aim to cure or treat cerebral palsy. A systematic review and meta-analysis summarizing and aggregating current research data may provide more conclusive evidence to inform treatment decision making and help direct future research. This review also helps to clarify which groups of patients are better suited to these treatments.

The objectives are as follows: (a) to assess the efficacy of stem cells (of any type) for improving the motor function of people with cerebral palsy, (b) to assess the efficacy of stem cells (of any type) for improving the cognitive function of people with cerebral palsy, and (c) to assess the safety of stem cell transplantation or transfection in this group of people.

MATERIALS AND METHODS

Criteria for Considering Studies for This Review

Types of Studies, Participants, and Interventions

We included randomized controlled trials (RCTs) and controlled trials, with or without blinded outcome assessment, that compared the outcomes of interventions with stem cells of any type versus standard care or no treatment at all or placebo (controls), in people with cerebral palsy. We included studies of humans with cerebral palsy. We did not apply any age, gender, severity of motor impairment, or race restrictions. We included comparisons of outcomes after all types of stem cell transplantation or transfection (allogeneic or autologous) versus standard care or no intervention or placebo (controls).

Types of Outcome Measures

Primary Outcome. Gross motor function was the primary outcome because physical disability is the chief presenting problem in cerebral palsy. Since improvements in motor function from conventional therapies are small, gains in motor function from a new therapy may provide a clear advantage.

Secondary Outcomes. Cognitive function was a secondary outcome because half of all children with cerebral palsy have an intellectual disability, which lowers the likelihood of employment and independent living plus elevates the risk of premature death [5]. Rates and types of adverse events were also examined to shed
light on the risk:benefit ratio of stem cell transplantation to inform patient decision making.

Search Methods for Identification of Studies

Electronic Searches
We developed a search strategy conforming to the recommendations of the Cochrane Handbook of Systematic Reviews of Interventions [17]. Our comprehensive search used the highly sensitive search filter for randomized controlled trials [17] to identify both published and unpublished trials, with no restriction on language or study years. Search terms are described in supplemental online Table 1.

The following electronic databases were searched: (a) Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, latest issue), (b) MEDLINE (from 1950 to October 2015), and (c) EMBASE (from 1950 to October 2015).

Searching Other Resources
A hand search of the reference list of included studies identified in the electronic searches was also conducted. In addition we electronically and manually searched the conference proceedings of the American Academy of Cerebral Palsy and Developmental Medicine, the Australasian Academy of Cerebral Palsy and Developmental Medicine, the European Academy of Childhood Disability, the Pediatric Societies of America, and the International Child Neurology Association Conference to include any gray literature (from 1980 to October 2015). We searched the Internet for information on ongoing trials and request information from study investigators to include within the review, e.g., http://www.clinicaltrials.gov/ (accessed October 15, 2015).

Data Collection and Analysis

Selection of Studies
Two review authors (I.N. and K.W.) independently reviewed the titles and abstracts of studies identified from the aforementioned sources. At title and abstract screening we excluded ineligible studies. If the title or the abstract did not provide sufficient information to determine eligibility, two independent reviewers appraised the full texts. We planned that if there were any disagreements on which articles met inclusion, we would invite a third reviewer to resolve disagreements. We planned that where multiple publications were reporting on the same study, only the relevant data would be extracted and included once.

Data Extraction and Management
Two review authors independently extracted the data from the included studies, using the Cochrane methodology [17], extracting citations, methodology, participants, interventions, outcomes, adverse events, and trial limitations. There was agreement on all extracted data.

Risk of Bias
Two review authors independently assessed risk of bias, using the Cochrane criteria [17]. There were no disagreements. The following methodological attributes were critiqued: (a) sequence generation; (b) allocation sequence concealment; (c) blinding of participants, treating clinicians, and outcome assessors; (d) incomplete outcome data; (e) selective outcome reporting; and (f) other potential threats to validity. The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach [18] and the PEDro Scale, which has established reliability providing a score out of 10 [19]. Quality ratings allowed objective comparisons of trials. We also summarized study limitations and any imprecision of the evidence that might have affected the outcomes reported.

Data Synthesis and Measures of Treatment Effect

Results were presented in a summary of findings table [17]. A priori we planned to perform a meta-analysis. We planned that if two or more included studies had comparable demographics and outcomes, the mean differences of outcomes would be pooled using Review manager software (RevMan5), to provide a summary estimate of a stem cell’s effects. For continuous outcomes with comparable units, effects were expressed as mean differences with 95% confidence intervals. For continuous outcomes with different units, effects were expressed as standardized mean differences (SMD) with 95% confidence intervals. Analysis was conducted at the individual allocation level because we included studies that used parallel group designs where participants had been randomized (or assigned) to interventions. We assessed heterogeneity of treatment effects between trials, using chi-square with a significance level at \( p < .05 \). We considered \( I^2 > 25\% \) moderate heterogeneity and \( I^2 > 75\% \) high heterogeneity.

RESULTS

Results of the Search
Results of the search are reported in a PRISMA flow diagram (Fig. 1) [20]. The initial search was carried out in October 2013 and updated in October 2015. The electronic and hand searches elicited 144 references. After screening, 41 studies were potentially eligible. After inspecting full texts, 5 studies met eligibility. Reasons for exclusion are summarized in the flow diagram. The 5 included trials studied 328 participants with cerebral palsy. Studies meeting inclusion criteria were all published in English. No data were missing and so no contact with authors was needed.

Included Studies

Types of Study Designs
We included four RCTs [21–24] plus one nonrandomized clinical trial (CT) [25] that evaluated the short-term effectiveness of stem cell intervention for improving the gross motor function of people with cerebral palsy. Three of the five studies compared stem cells with rehabilitation to rehabilitation alone [21, 23, 25]. One trial was a three-group RCT comparing (a) stem cells plus erythropoietin plus rehabilitation versus (b) erythropoietin plus rehabilitation versus (c) rehabilitation alone [24], whereas one trial compared stem cells alone to placebo [22].

Types of Participants
All five studies included 100% of participants with the diagnosis of cerebral palsy. Only one study specified which subtypes of cerebral palsy were included [23], which were spastic, dyskinetic, and mixed. Three of the five studies specified the participant’s gross motor function level at enrollment: all GMFCS levels were
included in Kang and Luan’s studies [22, 23], whereas Chen’s 2013 study [25] focused on those with more severe physical disability—levels III–V. The age range of participants varied. Three trials studied children less than 12 years old [21, 23, 24], whereas, two trials studied both children and adults simultaneously [22, 25].

Types of Intervention

All five studies aimed to improve the gross motor function using stem cells plus or minus rehabilitation, allowing meta-analysis. Two studies aimed to improve cognitive function and collected cognitive data [22, 24]. The types of stem cells implanted varied and included olfactory ensheathing cells (OECs), NSCs, NPCs, and allogeneic UCBs. Umbilical cord blood was delivered by both intravenous and intra-arterial transfusion, whereas the OECs, NSCs, and NPCs were neurosurgically transplanted directly into the central nervous system: either the spine or the brain since OECs, NSCs, and NPCs do not cross the blood–brain barrier readily. Given the varied cell types and varied doses of cells meta-analysis of dose effects was not possible. Type of cells, origin of cells, dose, transplantation method, and concomitant use of immunosuppression are summarized in Table 1. The rehabilitation was described with insufficient detail to allow replication in future studies. The stem cells used in the included trials for cerebral palsy, the mechanism of action [10, 12], the supporting preclinical [10, 12, 26–28] and therapeutic evidence [21–25], and associated risks [10, 12] are summarized in Table 2.

End Points

Two of the five trials measured a short-term 1-month after transplantation/transfusion end point, whereas the other trials measured at 3–6 months post-transplantation. Only one trial measured 12-month outcomes. The outcome data at each end point for each trial are summarized in Table 1. Only one single common data point existed between the trials (6 months post-transplantation) and was therefore used in the meta-analysis.

Types of Outcomes Measured

All five trials measured the effect of stem cells on gross motor function, using the Gross Motor Function Measure (GMFM), with one trial reporting the data in the alternative Gross Motor Performance Measure (GMPM) format. The GMFM data were treated as a continuous variable for analysis.

Effects of Interventions

Effect on Gross Motor

All five trials narratively reported benefits from stem cell intervention on gross motor function, as measured on the GMFM. Four of five trials reported statistically significant between-group differences on GMFM favoring stem cell intervention, but one trial did not calculate between-group differences [23]. Overall, stem cells with or without rehabilitation had a greater effect on gross motor function (as measured on the GMFM) than rehabilitation alone, SMD = 1.27 [95% CI 0.22–2.33] (Fig. 2A). However, there was significant heterogeneity between studies ($I^2 = 92$%). In addition, some trials collected extra motor data before and after stem cell intervention, including strength measured on the manual muscle test [22], fine motor function measured on the Peabody Developmental Motor Scales (PDMS) [23], and developmental motor measured on the Bayley Scales of Infant Development (Version III) [24]. These data were heterogeneous and could not be pooled.

Umbilical cord blood was used in two studies and was pooled for separate analysis. Umbilical cord blood, with or without rehabilitation, had a greater effect on gross motor function (as measured on the GMFM) than rehabilitation alone, SMD = 2.62 [95% CI 1.51–3.74], but with significant heterogeneity ($I^2 = 73$%). The forest plot (Fig. 2B) summarizes the UCB studies.

Effect on Cognition

Two studies collected cognitive outcome data [23, 24]. Both sets of cognitive data had high risk of bias and were of insufficient quality for pooling. One trial collected cognitive outcomes on an invalidated investigator-designed instrument [23]. The other trial used the Bayley II rather than the updated Bayley III [24].

Ongoing Studies

We are aware of one ongoing RCT that had completed primary end-point data collection, which would have met the criteria for inclusion in this review. Contact was made with the investigators but no outcome data were available at the time of writing. Further information about this study is available at https://clinicaltrials.gov/ct2/show/NCT01147653?term=Kurtzberg&rank=3.

Risk of Bias in Included Studies

The risk of bias in the five included studies was variable and has been summarized in Table 3. Table 3 also includes a summary of
| Citation       | Country     | Method          | Participants                                      | Intervention                                                                 | Cell type       | Cell dose                        | Cell source                        | Transplant method | Donor matching | Immuno suppression | Outcomes                                                                 |
|----------------|-------------|-----------------|--------------------------------------------------|-------------------------------------------------------------------------------|-----------------|----------------------------------|-----------------------------------|-------------------|----------------|------------------|--------------------------------------------------------------------------|
| Chen et al.    | China       | RCT             | Cerebral palsy                                   | Group 1: Stem cell + rehabilitation (n = 18)                                  | OECs            | Single dose 2 × 10^6 OECs, in 100 ml of medium | Allogeneic: Aborted human fetal olfactory bulb injected into the bilateral corona radiata in the frontal lobe of the brain | None              | Yes            | Matching not described   | At 6 months: Motor: Improved motor on GMFM-66 favoring stem cell group (p = .04) Care: No differences between groups for reduced caregiver burden on Caregiver Questionnaire Scale (NS, p = .09) |
| Chen et al.    | China       | Clinical trial, nonrandomized | Cerebral palsy                                   | Group 1: Stem cell + rehabilitation (n = 30)                                  | NSC-like cells  | 2 doses, 3 weeks apart, 1–2 × 10^7 of NSC-like cells in 5-ml cell suspension | Autologous: Bone marrow MSCs cultured and propagated in vitro until differentiated into NSCs | N/A               | None           | None              | At 1, 3, 6 months: Motor: Improved motor on GMFM-66 favoring stem cell group, 1 month (NS, p = .09), 3 months (NS, p = .01), and 6 months (p = .01) Language: No differences between groups for language on Gesell LDQ 1 month (NS, p = .75), 3 months (NS, p = .52), and 6 months (NS, p = .30) |
| Kang et al.    | South Korea | RCT             | Cerebral palsy                                   | Group 1: Stem cell (n = 17)                                                   | UCB             | Single dose >2 × 10^7/kg of UCB | Allogeneic: Donor UCB from cord blood bank | Intravenous infusion and Intra-arterial infusion | <2 HLA disparities | i.v. cyclosporine administered 2×/day for 3 days; oral cyclosporine administered daily for 9 days; i.v. solumedrol ×1 dose | At 1 and 3 months: Motor: Improved muscle strength on manual muscle testing (p < .05). At 6 months: Motor: Improved motor on GMFM-66 favoring the stem cell group (p < .05). Those who received a higher cell dose (which cannot be controlled using UCBs) had higher outcome scores. |
| Citation                  | Country   | Method     | Participants | Intervention                                                                 | Cell type       | Cell dose                                                                 | Cell source                                                                 | Transplant method                                                                 | Donor matching | Immuno suppression | Immunosuppression | Outcomes                                                                 |
|--------------------------|-----------|------------|--------------|-----------------------------------------------------------------------------|-----------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------|----------------|-------------------|----------------|-------------------------------------------------------------------------|
| Luan et al. [23]         | China     | RCT        | n = 94       | Cerebral palsy Subtype: Spastic, dyskinetic, and mixed Severity: GMFCS I-V Age: 0-3.5 years | Group 1: Stem cell + rehabilitation (n = 45)                  | NPCs                                                      | Single dose 8-10 × 10^6 of NPCs in 200 ml normal saline                            | Injected using ultrasound guidance into the lateral ventricles of brain through unclosed fontanelle or burr hole | No             | None               | None            | At 1, 6, and 12 months: Motor: Improved motor on GMFM-66 and PDMS-FM for stem cell group; however, between-group analysis not provided. At 12-months: Improved motor, fine motor, and cognition on an investigator-developed nonvalidated checklist, favoring the stem cell group (p < .001) |
| Min et al. [24]          | South Korea | RCT        | n = 105      | Cerebral palsy Subtype: Not defined Severity: Not defined Age: 10 months to 10 years | Group 1: Stem cell + erythropoietin + rehabilitation (n = 35) | Single dose 3 × 10^7/kg of UCB | Umbilical cord blood (UCB)                                                   | Intravenous infusion                                                                   | UCB group received cyclosporine intravenously 2×/day for 1 week + oral cyclosporine for 3 weeks | Yes: 4–6/6 HLA match | At 6 months: Motor: Improved motor on GMFM (p < .010) and BSID-II Motor scale (p < .002) favoring the stem cell group Cognition: Improved cognition on the BSID-II Mental (p < .008) and the “social cognition” scale in WeeFIM (p < .013) |
Long-term safety in cerebral palsy is unknown. Autologous UCB is assumed to be probably safe given the decades of long-term safety data in hematologic applications. Allogeneic UCB appeared relatively safe in the two included clinical trials [22, 24] but the theoretical risk of graft-versus-host (GVH) disease exists, even though GVH is considered unlikely to occur in people with cerebral palsy with healthy immune systems. Long-term safety in cerebral palsy is unknown. Assumed to be low risk because they have historically been assumed to be immune privileged, although this knowledge is evolving.

Two included clinical trials [22, 24] reported short-term motor gains in children with cerebral palsy but high risk of bias existed. Comment: MSCs are more likely to be helpful for infants with cerebral palsy during the early acute and inflammatory brain injury phase, e.g., in neonatal stroke and hypoxic-ischemic encephalopathy. Cerebral palsy clinical trials using adult NSCs with immunosuppression but safety is unknown for NPCs or NSC-like cells and therefore monitoring should occur using neuroimaging. Neurosurgical and infection risks exist from the transplantation procedure. Tumorigenic risks have not been observed in phase 1 trials using adult NSCs with immunosuppression but safety is unknown for NPCs or NSC-like cells and therefore monitoring should occur using neuroimaging.

### Table 2. Cell types and mechanisms of action, supporting evidence, and associated risks

| Citation           | Cell types and description | Assumed mechanism of cell action for cerebral palsy | Preclinical evidence in cerebral palsy | Therapeutic evidence in cerebral palsy | Associated risks |
|--------------------|-----------------------------|-------------------------------------------------|----------------------------------------|----------------------------------------|------------------|
| Chen et al. [21]   | OECs                        | Mechanism unclear a. Regenerative: OECs ensheathe axons in the olfactory receptors, and it is hypothesized they might have this remyelination action in the brain [21] b. Anti-inflammatory: Assumed no c. Tropic: Assumed yes to promote tissue sparing and stimulate endogenous repair [21] | Unknown in cerebral palsy but spinal cord animal model data exist | One included clinical trial [21] reported short-term motor gains in children with cerebral palsy but high risk of bias existed | Safety in cerebral palsy unknown |
| Chen et al. [25] and Luan et al. [23] | NSCs and NPCs | Mechanisms proposed to include a. Regenerative: NSCs make myelin and it is hypothesized they might remyelinate an injured brain or brain with arrested myelination from prematurity b. Anti-inflammatory: Assumed no c. Tropic: Assumed yes by stimulating other repair mechanisms | Rodent model: In the neonatal cerebral palsy stroke model and hypoxic-ischemic rat model NSCs reduce the severity of brain injury conferring neurobehavioral and motor gains [26] | Two included clinical trials [23, 25] reported short-term motor gains in children with cerebral palsy but high risk of bias existed | Neurosurgical and infection risks exist from the transplantation procedure. Tumorigenic risks have not been observed in phase 1 trials using adult NSCs with immunosuppression but safety is unknown for NPCs or NSC-like cells and therefore monitoring should occur using neuroimaging. |
| Kang et al. [22] and Min et al. [24] | UCB | Mechanism unclear [10, 12] a. Regenerative: UCBs cannot replace damaged brain cells but might support regeneration b. Anti-inflammatory: Assumed yes given UCB contains MSCs c. Tropic: Assumed yes since UCBs home to injured tissue and provide paracrine effects that might support regeneration Mechanism unclear [10, 12] a. Regenerative: MSCs cannot replace damaged brain cells but might support regeneration b. Anti-inflammatory: Assumed yes c. Tropic: Assumed yes since MSCs home to injured tissue and provide paracrine effects that might support regeneration, e.g., by sparing intrinsic cells and secretion of growth factors that stimulate repair processes | Rodent model: In the neonatal cerebral palsy stroke model and hypoxic-ischemic rat model UCBs reduce the severity of brain injury conferring neurobehavioral and motor gains [10, 12] Sheep model: In the hypoxic-ischemic sheep model for cerebral palsy, UCB prevents neuronal apoptosis [27] Rodent model: In the neonatal cerebral palsy stroke model, intranasal delivery of MSCs significantly reduces infarct size and gray matter loss [28] Primate model: MSCs transplantation leads to upregulation of IL-10 expression, plus a decrease in neuronal apoptosis and astroglial activity in the perischemic area [10] | Two included clinical trials [22, 24] reported short-term motor gains in people with cerebral palsy from autologous UCB transfusion. Cerebral palsy clinical trials using autologous UCB are under way but not yet complete Cerebral palsy clinical trials using MSCs are under way but not yet complete Comment: MSCs are more likely to be helpful for infants with cerebral palsy during the early acute and inflammatory brain injury phase, e.g., in neonatal stroke and hypoxic-ischemic encephalopathy. Causal pathways to cerebral palsy | Long-term safety in cerebral palsy unknown |

**Abbreviations:** MSC, mesenchymal stem cell; NPC, neural progenitor cell; NSC, neural stem cell-like; OEC, olfactory ensheathing cell; UCB, umbilical cord blood.
the quality ratings of the included studies and the trial limitations. The two trials using umbilical cord blood, from the same South Korean research group, used high-quality methodologies and had low risk of bias [22, 24].

**Adverse Events**

Serious adverse events associated with stem cell transplantation were reported from two of the five included trials [23, 24]. In two of the five trials, the details about adverse events were scant and considered insufficient, giving the potential risks [21, 25]. Neuroimaging was not performed in the trials where invasive stem cell transplantation techniques were used [21, 23, 25], and untoward adverse effects, like tumor growth, were therefore not adequately monitored. Adverse event details were most comprehensively reported in the Kang [22] and Min [24] trials. A summary of the rates of serious adverse events for each trial is described in Table 4. Serious adverse events included death of one participant in the stem cell group of Min’s trial. The cause of death was unknown. Of note, the participant had a seizure 24 hours prior to death, plus the family had not implemented the recommended nonoral feeding intervention.

The other n = 6 serious adverse events (AEs) recorded across all five trials were equally distributed across the stem cell and control groups. Fever was a nonserious adverse event that occurred equally across groups.

**DISCUSSION**

The objectives of this systematic review were to determine the effect of stem cell intervention for people with cerebral palsy on gross motor and cognitive function compared with rehabilitation or placebo. In addition, we wanted to review the safety of stem cell intervention by reviewing the numbers of adverse events. There were five trials (four RCTs and one nonrandomized trial) of stem cell interventions for people with cerebral palsy included in the review, with all studies providing sufficient data to be included in the primary outcome of the meta-analysis about gross motor effects. Meta-analysis demonstrated a positive short-term treatment effect for stem cell intervention on gross motor outcomes measured on the Gross Motor Function Measure. It is difficult to determine whether the size of the effect is of clinical significance because of the wide age ranges of the participants studied. Larger effect sizes are possible, expected, and needed in younger children for the result to be clinically meaningful, since their gross motor skills rapidly develop in childhood. Yet in the included studies, young children and adults were included within the same samples. The methodological decision to group children more than 5 years old with adults and compare this to children under 5 years old may have confounded study findings, since children’s gross motor potential plateaus after 5 years of age [29] and it would be reasonable to expect their capability to respond to this type of intervention might be different. Moreover, from a regenerative medicine perspective, it would be reasonable to expect better intervention responses from participants whose age was closer to the timing of the injury. Future studies should carefully consider gender and age at transfusion/transplantation as covariates and ultimately aim to treat younger patients.

An earlier systematic review investigated the effectiveness of stem cell intervention for people with cerebral palsy and concluded that “There were very few well-designed controlled clinical studies. There is a need for well-designed controlled
| Citation          | Random sequence generation: selection bias | Allocation concealment: selection bias | Blinding of participants and personnel: performance bias | Blinding of outcome assessment: detection bias | Incomplete outcome data: attrition bias | Selective reporting: reporting bias | PEDro trial quality score | GRADE quality rating | Study limitations                                                                 |
|-------------------|--------------------------------------------|----------------------------------------|----------------------------------------------------------|-----------------------------------------------|---------------------------------------|-----------------------------------|------------------------------|------------------------|-------------------------------------------------------------------------------------|
| Chen et al. [21]  | Low risk                                   | Low risk                               | Unclear risk                                             | Unclear risk                                  | High risk                             | High risk                         | 5/10                         | Low                    | Sample: Large number of dropouts ($n = 18/33$); $n = 7/33$ of intended sample not recruited; wide age range studied Design and analysis: Small sample size |
| Chen et al. [25]  | High risk                                  | High risk                              | High risk                                                | Low risk                                       | Low risk                              | Low risk                          | 5/10                         | Low                    | Design and analysis: Lack of randomization; small sample size Instruments: Validity of Gessell data collected in children too old for the instrument; redundancy of collecting the GMFM-88 data, when GMFM-66 also collected |
| Kang et al. [22]  | Low risk                                   | Low risk                               | Low risk                                                 | Low risk                                       | Unclear risk                          | Low risk                          | 8/10                         | High                   | Sample: Wide age range studied; placebo group median age is older and therefore may be less responsive to any intervention; unclear why $n = 2$ participants were excluded after randomization Design and analysis: Lack of rehabilitation protocol for both arms of the trial, when rehabilitation is standard of care (i.e., patients could have been worsening by natural history) Instruments: Manual muscle test validity in (a) 6-month-old children who cannot respond to commands and (b) people without the selective motor control to complete testing; validity of Bayley II, PEDI, weeFIM data collected in children and adults too old for the instrument’s upper age range; use of Bayley II, not Bayley III Intervention: Use of i.v. and i.a. infusion in the same study, resulting in some data needing to be excluded; confounding use of cyclosporine as an immunosuppressant, since cyclosporine might also have neuroprotective effects |
| Luan et al. [23]  | Unclear risk                               | Unclear risk                           | Unclear risk                                             | Low risk                                       | Low risk                              | High risk                         | 6/10                         | Moderate               | Design and analysis: Not stated if participants were blinded; no between-group analysis conducted for standardized measures Instruments: Use of an author-devised cognitive assessment test, which had unknown psychometric properties |
| Min et al. [24]   | Unclear risk                               | Low risk                               | Low risk                                                 | Low risk                                       | Low risk                              | Low risk                          | 9/10                         | High                   | Design and analysis: Lack of a UCB + rehabilitation group to allow examination of the effects of UCB; random sequence generation not described Instruments: Validity of Bayley II, PEDI, weeFIM data collected in children and adults too old for the instrument’s upper age range; use of Bayley II, not Bayley III Intervention: Confounding use of cyclosporine as an immunosuppressant, since cyclosporine might also have neuroprotective effects |

Abbreviations: GMFM, Gross Motor Function Measure; PEDI, Pediatric Evaluation of Disability Inventory; UCB, umbilical cord blood; WeeFIM = Wee Functional Independence Measure.
studies with more objective outcome measures” [30]. Dartnell’s [30] systematic review, however, did not include all the high-level evidence clinical trials we identified in our comprehensive search nor did it include a meta-analysis and therefore our update was warranted. To our knowledge, this is the first meta-analysis of stem cell interventions for people with cerebral palsy.

Our review and meta-analysis have a number of limitations concerning stem cell intervention. The experimental stem cell interventions in this review varied in terms of the types and ages of participants that received intervention, the types of cells used, the types of transplant/transfusion methods used, the cell doses, the theoretical rationale for why the cells might offer a treatment effect, the type and intensity of concomitant rehabilitation, and the duration of follow-up. This resulted in significant levels of heterogeneity when pooling gross motor outcomes and, therefore, limits the conclusions that can be drawn from these results. In addition, the studies measured only short-term benefits and the long-term effects remain unknown.

Different cognitive measurement tools were used in the studies, restricting the ability to pool data. It is possible either that these studies have no effect on cognitive outcome or that the measures did detect the effects of intervention but our interpretation of the meaning of these gains is cautious given the high risk of bias. There were fewer measurement tools used for assessing gross motor change than those used for assessing cognitive change, which made it possible to pool the motor data for meta-analysis.

The combined AE results conservatively suggest statistically comparable risks between groups (3% in the stem cell groups, 2% in the rehabilitation groups). Given the concern of the risks, continued safety monitoring post-transplantation or -transfusion is advised. All future trials should include detailed adverse event logs such as the one provided by Min et al. [24] and neuroimaging when invasive transplantation techniques are used. The cause of the one death was unknown. Fever equally occurred in both groups, but since fever can escalate to a serious health risk, monitoring after transplantation and transfusion is advised in future trials.

CONCLUSION

Our meta-analysis demonstrated that stem cell interventions for people with cerebral palsy have a small but significant short-term impact on gross motor skills. Stem cell intervention is not yet a cure, but has a larger treatment effect than rehabilitation alone. Rehabilitation, pharmacology, and orthopedic surgery are the current standard of care. The rate of serious adverse events reported in these trials was low (3% stem cells, 2% controls), suggesting an acceptable benefit:risk ratio. Further and longer-duration studies are therefore advisable to determine whether stem cell interventions might be an additive intervention that could be included within the cocktail of interventions that compose standard care.

Implications for Research

The result of the meta-analysis indicates that more stem cell research for cerebral palsy is worthwhile. Future clinical trials evaluating the effectiveness of stem cell intervention for cerebral palsy should use high-quality designs, sensitive measures, larger samples, and younger and more homogeneous patients closer to the timing of injury when considering age of transfusion/transplantation; measure whether gender affects outcomes; use well-matched allogeneic donor cells, nonconflating or no immunosuppression drugs, and more tightly controlled rehabilitation; measure long-term impact; and consider tractography as one outcome as well as neuroimaging to detect adverse events. Future cerebral palsy stem cell research studies should focus on mechanisms with supporting preclinical data, and human studies should be designed using the SPIRIT statement [31] and reported according to the CONSORT statement [32]. We have summarized cerebral palsy stem cell

Table 4. Rates of serious adverse events

| Citation       | Event       | Stem cell | Rehabilitation | Erythropoietin |
|----------------|-------------|-----------|----------------|----------------|
| Chen et al. [21]| Death       | 0/6       | 0/8            | N/A            |
|                | Other serious adverse event | 0/6 | 0/8 | N/A |
|                | Total (%)   | 0/6 (0)   | 0/8 (0)        | N/A            |
| Chen et al. [25]| Death       | 0/30      | 0/30           | N/A            |
|                | Other serious adverse event | 0/30 | 0/30 | N/A |
|                | Total (%)   | 0/30 (0)  | 0/30 (0)       | N/A            |
| Kang et al. [22]| Death       | 0/18      | 0/18           | N/A            |
|                | Other serious adverse event | 0/18 | 0/18 | N/A |
|                | Total (%)   | 0/18 (0)  | 0/18 (0)       | N/A            |
| Luan et al. [23]| Death       | 0/45      | 0/49           | N/A            |
|                | Other serious adverse event | 1/45 | 0/49 | N/A |
|                | Total (%)   | 1/45 (2)  | 0/49 (0)       | N/A            |
| Min et al. [24]| Death       | 1/35      | 0/34           | 0/34           |
|                | Other serious adverse event | 2/35 | 3/34 | 3/34 |
|                | Total (%)   | 3/36 (8)  | 3/34 (9)       | 3/36 (8)       |
| Total (%)      | 4/135 (3)   | 3/139 (2) | 3/36 (8)       |

Abbreviation: N/A, not applicable.
research progress to date and our recommendations for the field going forward in Figure 3.

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AUTHOR CONTRIBUTIONS

I.N.: conception and design, initial manuscript writing, data extraction, analyses, final approval of manuscript; K.W.: data extraction, critical analyses, review and revision of manuscript, final approval of manuscript; R.W.H., E.M.W., M.F., N.B.: critical review and revision of manuscript, final approval of manuscript.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

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