Stem cell therapy in improving the motor function of patients with cerebral palsy: Systematic review with meta-analysis

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Abstract

Background: Cerebral palsy (CP) has no cure yet. This study was aimed to evaluate the efficacy and safety of stem cell therapy (SCT) for improving the gross motor function (GMF) of patients with CP. ***Methods*****:** A systematic literature search was performed in CENTRAL, PubMed, Embase, and Google Scholar to identify relevant randomized controlled trials from the year 2012 to 2022. The outcome measures were GMF and adverse events. For the meta-analysis, treatment effects on GMF improvement were expressed as standardized mean differences (SMD) with 95% confidence intervals (CI), using a random-effects model.

Results*:* There were seven trials that either used autologous or allogenic stem cells, with 411 participants, and were met with inclusion and exclusion criteria. The age, severity, and type of CP in participants varied. Follow up duration ranged from 6 to 24 months. Four studies had single transplantation while the other three had two to four sessions. Overall, a significant positive effect on GMF was seen in SCT than control group, SMD = 2.22 [95% CI 1.15 - 3.29] with a high heterogeneity (I^2 = 95%). In a separate analysis, umbilical cord blood (UCB) was the most effective cell type, SMD = 3.24 [1.38,5.10]. Serious adverse events were rare, with similar effects in treatment and control groups.

Conclusion*:* A positive and safe effect of SCT, specially UCB on GMF, was observed. However, the standardizations of treatment regimes, therapeutic-cell dose, and SCT optimal timing are needed to maximize the efficacy of treatment.

Keywords: Cell Therapy, cerebral palsy, efficacy, motor function, movement disorders, stem cell

INTRODUCTION

Cerebral palsy (CP) is the most prevalent physical disability in children, affecting mobility, posture, and balance. It stems from a child's abnormal brain development or brain injury. Globally, there are 2.1 cases of CP for every 1000 live births.[1] The cause for most of the babies born with CP is still undetermined. Learning challenges, difficulty walking, eating, and speaking are among the common impairments experienced by patients with CP.[2] The level of CP severity varies from case to case and can be classified by gross motor function using the Gross Motor Function Classification System (GMFCS).[3]

Although CP is incurable, individuals may benefit from conventional therapy, including occupational therapy, physical rehabilitation, and speech therapy, depending on the type and severity of their condition. Researchers are now investigating the safety and benefits of stem cell therapy for individuals with cerebral palsy. While there are a number of novel applications of stem cells being studied, none of them offer a full recovery. Numerous cell types, such as neural precursor cells, mesenchymal stem cells, induced pluripotent stem cells, and embryonic stem cells, have been employed.4–7 Because of their capacity for regeneration, cell transplantation has demonstrated encouraging results for issues with the central nervous system.[5,8] Stem cell therapy for cerebral palsy patients aims to promote injured cells' chances of survival, aid in their healing, and prevent long-term harm. Stem cells have been the general goal of stem cell therapy in CP patients is to maximize the likelihood of damaged

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cells surviving, encourage their recovery, and prevent permanent harm. Clinical trials and animal models have both evaluated the safety and effectiveness of using stem cells to treat cerebral palsy (CP), with encouraging outcomes. The potential benefits of stem cell therapy in CP can be obtained by either or combination of the following pathways:
(i). replacement of the damaged or lost neurons and oligodendroglia, (ii). Paracrine mechanism wherein different factors such as growth factors and anti-inflammatory factors release and stimulate the recovery of injured cells in the brain. Stem cells can (i). enhance the neuroregeneration by its homing properties, (ii). secret different active molecules, including trophic factors, neurotrophic factors, cytokines and soluble molecules, angiogenic factors. Also, patients with CP may get benefit from stem cell immunoregulation, neuroprotection, and neurodifferentiation.[9,10] Both autologous and allogenic stem cells have been used for CP treatment. Though autologous cells may seem more attractive due to little or less immunogenic and rejection concerns, allogenic cells are probably better, especially for preterm neonates.[11] Moreover, the goal of stem cell therapy is to promote central nervous system regeneration. Those with cerebral palsy may benefit from improved neuromotor function as a result. The purpose of this study was to evaluate the safety and effectiveness of stem cells in enhancing patients with cerebral palsy's gross motor performance.

METHODS

Search strategy and identification of studies

Clinical trials that used stem cell therapy in children with CP were retrieved from Google Scholar, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and PubMed databases by three reviewers independently between April to May 2022. Also, the reference lists of previous reviews and studies found in the above databases were manually checked.

Eligibility criteria

All randomised controlled trials (RCTs) involving human studies with patients with CP published in the English language from the year 2012 to 2022 were included. The eligibility criteria were showed in PICOs framework (Table 1).

Types of studies, participants, and interventions

Only randomized control trials (RCTs) with intervention groups (all types of stem cell therapy) vs control groups (placebo, rehabilitation, or no intervention) were included. No limitations were placed on the age, kind, or severity of the CP. But news articles, editorials, and other popular media were omitted. A third, independent reviewer dealt with any apparent discrepancies in the selection procedure.

Types of outcome measures

Primary outcomes: The primary outcome of interest for stem cell therapy was an overall improvement in gross motor functioning in individuals with CP.

Secondary outcomes: The safety of stem cell therapy was examined by analyzing adverse incidents. This can give patients a reasonable assessment of the risk to benefit ratio of stem cell therapy when making decisions.

Assessment of risk of bias and data extraction

Two reviewers independently assessed the risk of bias in each included study using Cochrane's 'Risk of bias' tool.[12] Any disagreement was recorded and resolved by the involvement of an additional reviewer. Each trial was evaluated as low, high, or unclear risk of bias in the following areas: (i) allocation concealment;) (ii) random

Table 1: PICOs framework

Population (P)	People with cerebral palsy (Inclusion criteria were both genders, all age groups, all different types of CP with any severity level of functional limitations)
Intervention (I)	Stem cell therapy
Comparison (C)	Compare the outcomes after stem cells therapy versus placebo or rehabilitation (controls).
Outcome (O)	Gross motor function and adverse effects
Study (S)	All randomized controlled trials involving human subjects

sequence generation; (iii) blinding of outcome assessment; (iv) blinding of participants and personnel; (v) incomplete outcome data; and (vi) selective reporting.

Data collection and analysis

Selection of studies: Three independent reviewers critically evaluated each piece of literature to determine its overall quality. The Jadad score was used to evaluate quality. To be included in this study, an RCT had to receive a minimum score of 3.[13]

Data extraction and management: The data from the selected papers were retrieved using research tables. Extracted information also included study design, participants, adverse events, methodology, and interventions.

Measures of treatment effect: Statistical analysis was done using Review Manager 5.3 to provide a summary estimation of stem cell's effects. The mean, standard deviation, and the number of participants in stem cell treatment groups and control groups were used for the continuous outcome. The random-effects model was used. Different scales measured the same variable; thus standardised mean differences (SMD) with 95% CI were used to measure the treatment effect. For interpreting effect sizes or SMDs, 0.2, 0.5, and 0.8 were considered as small, moderate, and large effects subsequently.

Assessment of heterogeneity: When statistical heterogeneity was found, the impact of the heterogeneity was evaluated using Chi-square, with a significance level set at $p < 0.05$. Moderate heterogeneity was defined as an $I2 > 25\%$ and high heterogeneity as an $I2 > 75\%$. The evaluation of research features heterogeneity encompassed variances in participant demographics, techniques, and stem cell types employed.

RESULTS

Results of the search

The results of the search are provided in a PRISMA flow diagram (Figure 1).

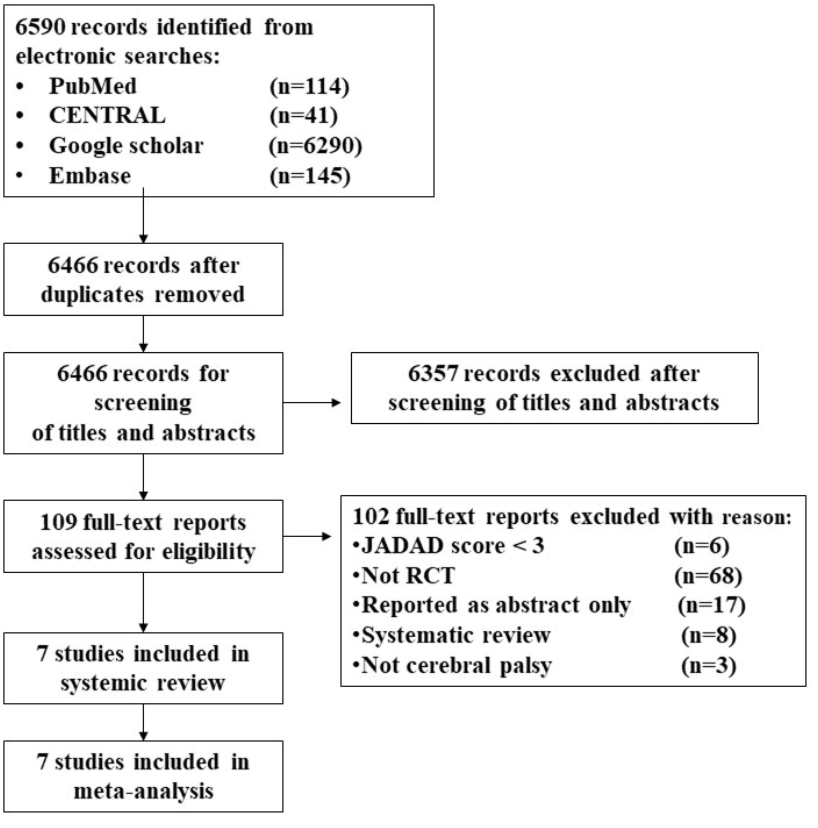

Figure 1. PRISMA flow diagram

A total of 6,590 references were retrieved, and 109 articles were considered as potentially eligible after screening. After assessing full texts, seven studies met eligibility. While 102 articles excluded with reasons summarized in Figure 1.

Included studies

All seven RCTs had a quality assessment of JADAD scoring ≥ 3 points. These studies randomly assigned their participants to the experimental group, which received the stem cell intervention and a control group that received conventional treatment such as rehabilitation or placebo. The follow-up duration of the studies was 6months to 2 years. The characteristics of the selected trials are summarized in Table 2.

Characteristics of participants

All seven trials included a total of 411 participants with a diagnosis of CP. Most of the participants were male. The age, severity, and type of cerebral palsy was different in all participants. In these trials, participants were less than 12 years old, except for one trial.[18] The type of cerebral palsy was only recorded in three trials.[14,17,18] Four trials recorded the severity of CP in GMFCS at baseline.[16-18]

Types of intervention

One trial compared stem cells alone to placebo.[16,17] Two trials compared stem cells with rehabilitation to rehabilitation alone.[14] Two trials compared stem cells with rehabilitation to placebo with rehabilitation.[19,20] Two RCTs were a three-group comparing with additional effect compared to erythropoietin[19] or mononuclear cells.[18] Out of the seven trials, the transplanted cells utilized in five trials were derived from umbilical cord blood (UCB)[15,17,19,20], while one trial was from bone marrow mesenchymal stem cells and bone marrow mononuclear cell[18], and one was neural progenitor cells.[14] Five trials used allogeneic stem cells[14,16-18,20], and 2 trials used autologous stem cells.[15,19] The chosen trials used a variety of techniques for cell transplantation, the majority of which used intravenous infusion. The details of the intervention plan of selected trials are summarized in Table 3.

Type of outcomes measured

All seven trials measured the effect of stem cell intervention on GMF, using the Gross Motor Function Measure (GMFM), allowing meta-analysis. The data were analysed as a continuous outcome. Details of the outcome of selected trials are summarized in Table 3.

Effects of interventions on gross motor function

Significant improvements in GMF14–16, 18–20 were found in six of the seven studies. Patients who got a larger cell dose (>2 x 107/ kg) demonstrated statistically significant improvements compared with those who received lower doses, while one experiment found no significant differences in mean changes between treatment and control groups17 (Table 3).

Overall, a positive effect on GMF was observed in stem cell group compared to control group, SMD = 2.22 [95% CI 1.15, 3.29] (Figure 2). However, the test for heterogeneity was statistically significant (Chi^2 = 119.24, $p < 0.001$; I^2 = 95%). UCB was pooled for independent analysis since it was the most frequently used stem cell in the chosen trials. Compared to the control group, UCB showed a higher treatment impact on GMF, SMD = 3.24 [95% CI 1.38, 5.10] (Figure 3) but with significant heterogeneity (Chi^2 = 113.62, $p < 0.001$, I^2 = 96%).

The follow-up time varied between these research, with the most available GMFM data being 6 or 12 months. As a result, it was divided into 6- or 12-month intervals for individual analysis. At 6-months, there was a more positive treatment effect favoring stem cell therapy SMD 3.33 [95% CI 1.59,5.07]. The Forrest plots of GMF changes at 6- or 12-months period in the selected studies are presented in the supplementary material.

Risk of bias

The risk of bias in selected trials was assessed using the Cochrane criteria. The risk range was variable. Three selected trials that used UCB had high-quality methodologies with Jadad score 5 and had a low risk of bias.[15,16,20]

The summary of the risk of bias in the selected studies is presented in supplementary materials.

Adverse events (AE)

Two of the seven trials reported serious adverse events (SAE).[14,15] In one trial, 10 SAE were reported that required patient hospitalization, such as pneumonia, seizure, influenza, and urinary

Table 2: Details of intervention plan of selected studies

Study	Participants	Intervention	Stem Cell Used	Mode of delivery	Frequency
Luan *et al.* 2012[14]	Cerebral palsy Type: quadriplegic, diplegic, dyskinetic, mixed Severity: GMFCS I-V Age: 0-3.5 years	Group 1: Stem cell + rehabilitation (n=45) Group 2: Rehabilitation (n=49)	Allogeneic neural progenitor cells derived from aborted fetal tissue	Injected into lateral ventricles of brain through fontanelle under guidance of ultrasonography.	Single transplantation session
Min *et al.* 2013[15]	Cerebral palsy Type: Not defined Severity: Not defined Age: 10 months - 10 years	Group 1: Stem cell + erythropoietin + rehabilitation (n=35, n=4 dropouts) Group 2: Erythropoietin + rehabilitation + placebo (n=36, n=3 dropouts) Group 3: Rehabilitation + placebo (n=34, n=2 dropouts)	Allogeneic umbilical cord blood	Intravenous infusion	Single transfusion session
Kang *et al.* 2015[16]	Cerebral palsy Type: Not defined Severity: GMFCS I-V Age: 6 months -20 years	Group 1: Stem cell + rehabilitation (n=17) Group 2: Rehabilitation (n=17)	Allogeneic umbilical cord blood	Intravenous infusion or intra-arterial infusion	Single transfusion session
Sun *et al.* 2017[17]	Cerebral palsy Type: quadriplegia, diplegia, hemiplegia Severity: GMFCS I-IV Age: 1-6 years	Group 1: Stem cell (n=32) Group 2: Placebo (n=31)	Autologous cord blood	Intravenous infusion	Single transfusion session
Liu *et al.* 2017[18]	Cerebral palsy Type: Spastic Severity: GMFCS II-V Age: 6-150 months	Group 1: BMMSCs (n=35, n=2 dropouts) Group 2: BMMNCs (n=35, n=1 dropouts) Group 3: Rehabilitation (n=35)	Autologous 1) Bone marrow mesenchymal stem cells (BMMSCs), 2) Bone marrow mononuclear cell (BMMNCs)	Intrathecal	4 transplantation session at an interval of 3-4 days

Table 2: Details of intervention plan of selected studies (Continued)

Study	Participants	Intervention	Stem Cell Used	Mode of delivery	Frequency
Huang *et al.* 2018[19]	Cerebral palsy Type: Not defined Severity: Not defined Age: 3-12 years	Group 1: Stem cell + rehabilitation (n=28, n=1 dropouts) Group 2: Rehabilitation + placebo (n=28, n=1 dropouts)	Allogeneic human umbilical cord blood mesenchymal stem cell	Intravenous infusion	Total 2 cycles. 4 infusion in each cycle at an interval of 7 days between infusions, and 3 months interval between cycles.
Gu *et al.* 2020[20]	Cerebral palsy Type: Not defined Severity: Not defined Age: 2-12 years	Group 1: Stem cell + rehabilitation (n=20, n=1 dropouts) Group 2: Rehabilitation + placebo (n=20)	Allogeneic umbilical cord-derived mesenchymal stem cell (hUC-MSCs)	Intravenous infusion	4 transfusions at an interval of 7 days

tract infection, but the distribution of adverse effects did not differ between the treatment and control groups.[15] The same study also reported one death that was determined to be unrelated to treatment after all records and events were reviewed. Non-serious AE such as fever, urticaria, and diarrhoea was often reported after treatment. Few patients who received intrathecal injections reported headaches, nausea, and vomiting, attributed to effect of lumbar puncture. However, these complications were transient in nature and symptomatically managed successfully. There were no prolonged or delayed adverse effects reported throughout the varied duration of studies. Details of the AE are summarized in Table 3.

DISCUSSION

The specific mechanism of action for stem cell treatment in CP is still unknown. Because of the blood-brain barrier, injected stem cells are less likely to migrate to the brain and differentiate into neural cells. However, the trophic and anti-inflammatory properties of stem cells are well understood and may explain some of the reported benefits. According to a recent study, psychological alterations were the most frequently recognized benefits after stem cell therapy in patients with CP.21 The psychological alterations may be related to the reported success of stem cell therapy for enhancing the motor function of patients with CP in the current study.

The observed improvement in GMF in all seven trials included in this study could be explained by stem cells' paracrine mechanism, which secretes a variety of cytokines such as anti-inflammatory cytokines, neurotrophic factors, and angiogenic factors.

All selected trials in this review have provided sufficient data for the outcome measured with meta-analysis. A positive treatment effect on GMF was established based on this meta-analysis for stem cell intervention. However, these seven included trials indicted a significant heterogeneity when the GMF outcome was pooled. These might be the result of different treatment protocols, such as methods of cell transplantation, type of stem cells used, age of patients, severity, and type of CP, cell doses, duration of follow-up, treatment phases, and gap period. Therefore, the conclusions that can be drawn from the results are limited.

Table 3: Details of outcome of selected studies

Study	Follow-up Duration	Outcome	Serious Adverse Events (SAE) & Adverse Events (AE)
Luan *et al*. 2012[14]	12 months	At 1 and 6 months: Motor: significantly improved on GMFM and PDMS-FM in stem cell group ($p<0.01$). At 12 months: Significantly improved in motor, fine motor and cognition on an unified survey questionnaire in the stem cell group ($p<0.001$).	SAE: 1 patient developed small foci bleed in the frontal lobe at puncture side, manifesting in low-grade fever and mild right-sided facioplegia, which resolved within 2 weeks after coagulant and symptomatic treatment. AE: 6 patients developed non-bacterial fever lasting about a week. No prolonged or delayed adverse effects were reported.
Min *et al*. 2013[15]	6 months	At 6 months: Motor: significantly improved on GMPM ($p<0.01$), and BSID-II Motor scale ($p<0.002$) in stem cell group. Cognition: Significantly improved on BSID-II Mental ($p<0.008$), and social cognition of WeeFIM ($p<0.013$).	SAE: 10 SAE requiring hospitalization were reported. However, the incidence of SAE did not differ between groups. 1 death occurred after 3-month post-treatment, but was concluded not to be related to treatment after all related records and events were reviewed. AE: Fever, upper respiratory tract infection, urticaria, diarrhoea and others. No prolonged or delayed adverse effects were reported.
Kang *et al.* 2015[16]	6 months	At 1, 3 months: Muscle strength: significantly improved on manual muscle testing in UCB group ($p < 0.05$). At 6 months: Motor: Significant improved on GMFM-66 in UCB group ($P<0.01$). Those who received a higher cell dose $\geq$ 5.46 x 107/kg showed a higher outcome scores.	SAE: No SAE were reported AE: Upper respiratory tract infection, pyrexia, pneumonia and others. The incidence of AE did not differ between groups.
Sun *et al*. 2017[17]	24 months	At 1 year: Motor: no significant different in mean change in GMFM-66 between treatment and placebo groups ($p=0.99$). In 2-year analysis: Those who received a higher cell dose $\geq$ 2 x 107/kg showed significantly greater increases in GMFM-66, PDMS-2 and normalized brain connectivity.	SAE: No SAE were reported. AE: 1 patient had transient infusion reactions consisting of hives and low-grade fever after both placebo and ACB infusions, successfully treated with additional diphenhydramine. 1 ACB unit grew beta-hemolytic streptococcus from a sample of the thawed unit, the patient was not treated with antibiotics and did well.

Table 3: Details of outcome of selected studies (Continued)

Study	Follow-up Duration	Outcome	Serious Adverse Events (SAE) & Adverse Events (AE)
Liu *et al.* 2017[18]	12 months	At 3, 6 and 12 months: Motor: Significant improved on GMFM and FMFM scores were in the BMMSC group (P<0.05), higher than the BMMNC and the control groups.	SAE: No SAE were reported. AE: Fever (8.8% in BMMNC group and 6.1% in BMMSC group), low intracranial pressure reactions (17.6% in BMMNC group and 12.1 in BMMSC group).
Huang *et al.* 2018[19]	24 months	At 3,6,12 and 24 months: Motor: Improved motor on GMFM-88 in stem	SAE: No SAE were reported. AE: Upper respiratory tract infection, diarrhoea, anorexia, constipation and urticaria.
Gu *et al.* 2020[20]	12 months	At 1 and 3 months: Motor: not significant improved on GMFM- 88 in stem cell group (p=0.237, p= 0.062). At 6 and 12 months: Motor: Significant improved on GMFM-88 in stem cell group (p<0.05).	SAE: No SAE were reported. AE: Upper respiratory tract infection, diarrhoea, fever, vomiting, constipation. No significant difference between groups.

The limited number of cells available from a single unit remains a challenge in UCB.[23] For example, the number of infused stem cells present in the average UCB unit is only approximately 5% of the optimal dose for adults ($2–4 \times 10^6$ $CD34^+$/kg)[24]. The inability to achieve cell dose standardization is the limitation in many studies.[25] Sun *et al.*[17] reported that those who received a higher cell dose demonstrated significant improvement in GMF than those who received a lower dose. These similar findings were also reported in the other two trials.[15,16] However, the therapeutic cell dose has yet to be established, which should be further explored in future studies.

The optimal timing of stem cell therapy is still unknown. Few animal studies found that an early administered stem cell therapy had more significant neuroprotection.[26,27] Younger age at the time of treatment has been associated with better outcomes, but most of the cases with CP are not diagnosed until approximately 2 years of age. In some studies, both children and adults have been recruited; however, due to the likely effect of age on the outcome of stem cell treatment, this wide range of participants' age might be a confounding factor for the interpretation of results. Therefore, in future research, the age range and timing of receiving stem cell therapy should be appropriately planned for obtaining more precise results.

Adverse events were reported in all trials, with no prolonged or delayed adverse effects. The serious adverse events which were reported in Min, *et al.*[15] had an equal incidence in both treatment and control group. The detailed adverse effects and monitoring the safety of stem cell therapy for a long period are essential in future trials since the late complications of allogenic stem cell transplantation have been reported in some diseases.[28] It is also essential to study the biological characteristics of CP patients, such as

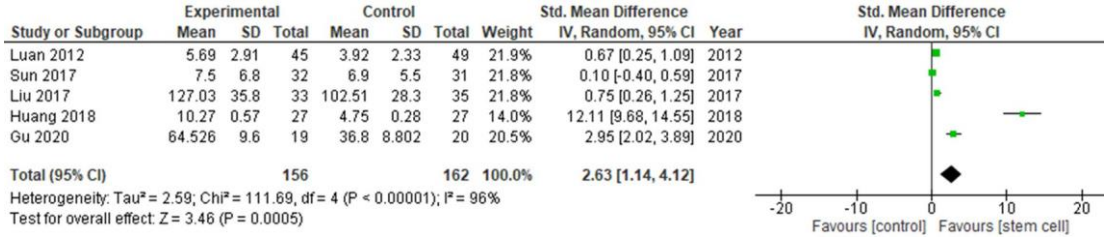

Figure 2. Forest plot of comparison: Intervention group compared to the control group, (Outcome: Gross motor function changes at 6 or 12 months) (RevMan version 5.3 was used to create the forest plot)

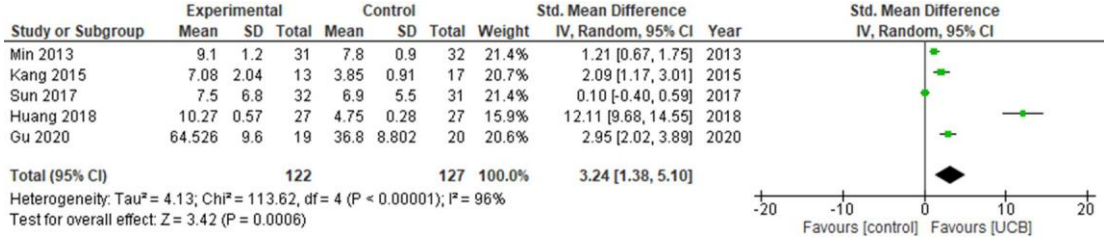

Figure 3. Forest plot of comparison: Umbilical cord blood compared to the control group, (Outcome: Gross motor function changes) (RevMan version 5.3 was used to create the forest plot)

their genetic makeup, since evidence exists, which links the safety of stem cell therapy outcomes with genetic variations.[29]

Conclusion

In conclusion, our study found that stem cell therapy has therapeutic effects on improving motor functioning in CP patients. Stem cell therapy looks to be safe, save for a few small and transitory side effects. However, the approaches for standardizing the greatest efficacy of stem cells, treatment regimens, therapeutic cell doses, and optimal timing of cell therapy remain uncertain. Additionally, patient selection for stem cell therapy is critical to ensuring safety and efficacy. Thus, future clinical trials should include longer follow-up periods and contain specific criteria such as patient age groups, gender, date of injury, severity, and type of CP. To reduce undesirable effects, strictly manage the safety of research by optimizing the route of distribution, kind of stem cell, and dosage. This may yield more trustworthy evidence for future treatment options. In the future, parents of patients diagnosed with CP may be given the choice of stem cell therapy as a biological intervention to improve their children's motor function.

Conflict of interest: None

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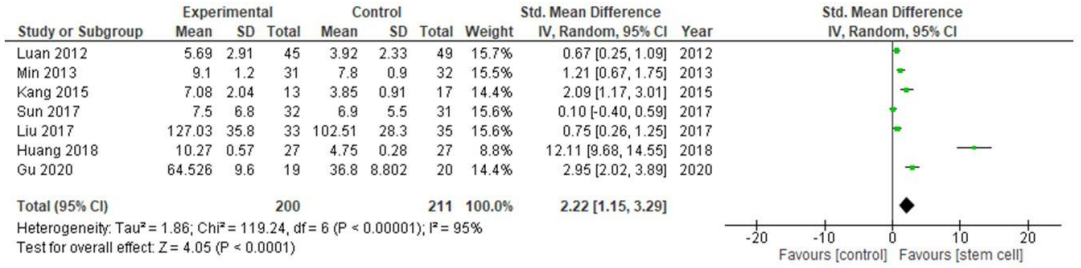
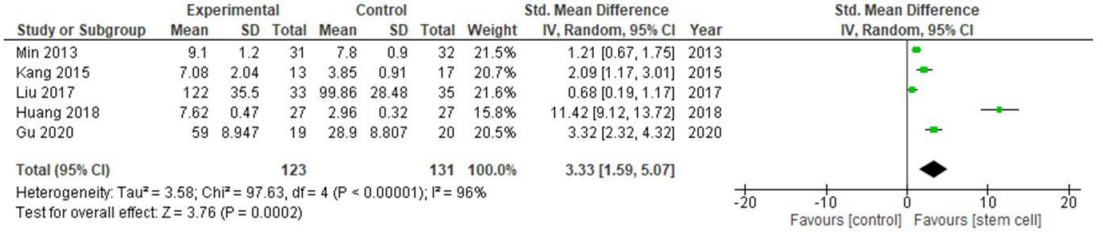
Supplementary



Supplementary Figure 1. Forest plot of comparison: Intervention group compared to the control group, Outcome: Gross motor function changes at 6 months (RevMan version 5.3 was used to create the forest plot)



Supplementary Figure 2. Forest plot of comparison: Intervention group compared to the control group, Outcome: Gross motor function changes at 12 months (RevMan version 5.3 was used to create the forest plot)

Summary of the risk of bias in the selected studies

	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)
Luan et al. 2012[14]	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	High risk
Min et al. 2013[15]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kang et al. 2015[16]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Sun et al. 2017[17]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Liu et al. 2017[18]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Huang et al. 2018[19]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Gu et al. 2020[20]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk