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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 2010 to 2020. The outcome measures were GMF and adverse events. For the meta-analysis, treatment effects on GMF improvement were expressed as standardised 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

The most common physical disability in childhood is cerebral palsy (CP), which affects posture, balance, and movement. It originates from brain injury or atypical brain development in the child. Overall, the incidence of CP is 2.1 in 1000 live births globally.[1] The cause for most of the babies born with CP is still undetermined. Patients with CP often have associated impairments, such as difficulty speaking, walking, eating, and learning disabilities.[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]

There is no cure yet, but patients with CP are often introduced to conventional therapy, such as occupational therapy, physical rehabilitation, and speech therapy, depending on the nature and severity of the disorder. Research in stem cell therapy for patients with CP is advancing, but researchers are still evaluating if these methods are safe and effective. Various new strategies for using stem cells are being studied, but none of them provides a full cure yet. Different types of cells have been utilized, such as embryonic stem cells, mesenchymal stem cells, neural precursor cells, and induced pluripotent stem cells.[4-7] Cell transplantation for central nervous system disorders has shown promising outcomes due to their regenerative ability.[5,8] The overall purpose of stem cell therapy in patients with CP is to increase the surviving chances of damaged cells, provide support for their recovery, and inhibit permanent damage. Stem cells have been

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explored for its efficacy and safety in treating CP in both animal models and clinical trials with successful results. The potential benefits of stem cell therapy in CP can be acquired via any or combination of the following mechanisms: (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]

Also, the concept of stem cell therapy is to stimulate the regeneration of the central nervous system. This may improve the neuromotor function of patients with CP. This study was done to evaluate the efficacy and safety of stem cells for improving the gross motor function of patients with CP.

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 2020. Also, the reference lists of previous reviews and studies found in the above databases were manually checked. Keywords used were stem cells, cerebral palsy, and gross motor function. Details of search terms are presented in Supplementary Material.

Eligibility criteria

All randomised controlled trials (RCTs) involving human studies with patients with CP published in the English language from the year 2010 to 2020 were included. The eligibility criteria were showed in PICOs framework (Table 1).

Types of studies, participants, and interventions

Only randomized control trials (RCTs) study designs involving intervention group (all types of stem cell therapy) compared with the control group (placebo or rehabilitation or no intervention) were included. No restrictions regarding age, type, or severity of CP were made. While editorials, newspaper articles, and other forms of popular media were excluded. A third, independent reviewer resolved any apparent discrepancies during the selection process.

Types of outcome measures

Primary outcomes: The primary outcome of interest for stem cell therapy was an improvement in gross motor function.

Secondary outcomes: Adverse events were evaluated to assess the safety of stem cell therapy. This can provide a fair judgment of benefit; risk ratio of stem cell therapy for patients' decision making.

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: All literature underwent critical appraisal to assess their quality by three reviewers independently. Quality assessment was carried out using the Jadad score. A minimum score of 3 was required for an RCT to be included in this study.[13]

Data extraction and management: Data were extracted from the selected articles using research tables. Also, methodology, participants, interventions, study design, outcome, and adverse events were extracted.

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: The impact of statistical heterogeneity was assessed using Chi-square with a significance level at $p < 0.05$ was used for identified statistical heterogeneity. An $I^2 > 25\%$ was measured as moderate heterogeneity and $I^2 > 75\%$ high heterogeneity. Heterogeneity of study characteristics, including differences in types of stem cells used, participants, methods, were also evaluated.

Ethical Statement

This study was registered in the National Malaysia Research Registry (NMRR-18-3148-45006).

RESULTS

Results of the search

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

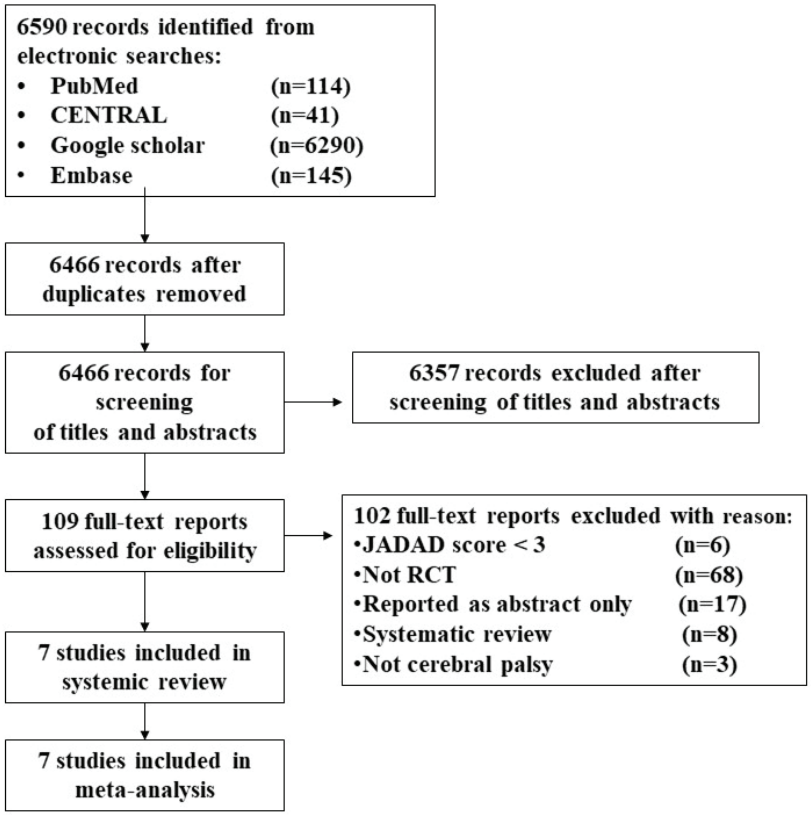

Figure 1. PRISMA flow diagram

initial search for this review in December 2018 and updated it again in April and May 2020. 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 were randomly assigned their participants to the experimental group, which received the stem cell intervention and a control group that received conventional treatment (rehabilitation or placebo). The follow-up duration of the studies was 6 to 24 months. 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. The trials were conducted in China[14,18,19], Korea[15,16], and the United States of America.[17] Most of the participants were male. The age, severity, and type of cerebral palsy in participants varied. In all 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] There were variations in the methods of cell transplantation that was performed in the selected trials, with most using 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

Six out of seven trials reported significant improvement of GMF[14-16,18-20]. One trial reported no significant difference in mean changes between treatment and control groups[17], but those who received a higher cell dose (>2 x 10^7/ kg) showed statistically significant improvements compared with patients who received lower doses (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%). Since UCB was the most used stem cell in the selected trials, it was thus pooled for separate analysis. A greater treatment effect on GMF was reported for UCB than control group, 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 period varied among these studies, with the most available GMFM data at 6- or 12- months. Thus, it was aggregated for individual analysis into 6- or 12- months. A greater positive treatment effect favouring stem cell therapy was noted at 6-months, 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 exact mechanism of action(s) of stem cell therapy in CP is still unknown. Due to the blood-brain barrier, it is less likely that injected stem cells can travel to the brain and differentiate to neuron cells. However, the trophic and anti-inflammatory effects of stem cells are well known and might partially explain the observed effects. A recent study has reported the psychological changes as the most frequent detected improvements after stem cell therapy in patients with CP.[21] The psychological changes might be associated with the reported efficacy of stem cell therapy for improving the motor function of patients with CP in the present study. The paracrine mechanism of stem cells with the secretion of a variety of cytokines, such as anti-inflammatory cytokines, neurotrophic factors, and angiogenic factors, may explain the observed improvement in GMF in all seven trials included in this review.

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.

In our review, the treatment effect was notably greatest for UCB cells compared to any other cell type. An earlier systematic review with meta-analysis[2] also had a similar finding that UCB cells have a greater effect than other cell

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 ≥ 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 ≥ 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 cell group (p = 0.000).	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.

types and concluded that patients with CP who have undergone stem cell intervention have a significant short-term effect on GMF. UCB cell therapy for the treatment of patients with CP is currently widely assessed in clinical trials, and some preclinical studies have shown that human cord blood-derived stem cells can induce endogenous nerve repair processes.[22] Although the precise action of mechanisms for neurogenesis and neuroprotective effects to sites of injury remains to be confirmed, the methodologies to standardize the maximum efficacy of UCB treatment regimens are still required.

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

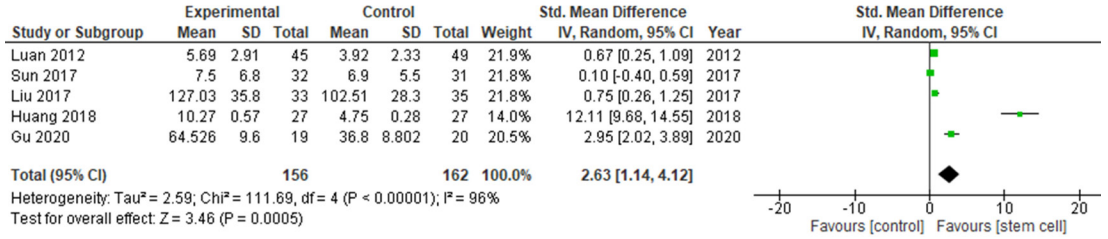

Figure 2. Forest plot of comparison: Intervention group compared to the control group, (Outcome: Gross motor function changes at 6 or 12 months) (RevMan version 5.3 was used to create the forest plot)

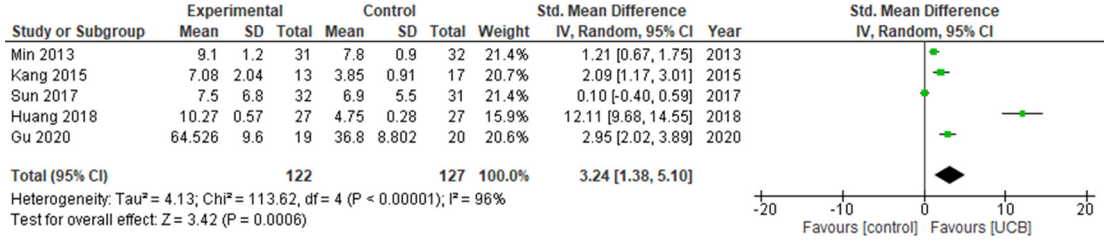

Figure 3. Forest plot of comparison: Umbilical cord blood compared to the control group, (Outcome: Gross motor function changes) (RevMan version 5.3 was used to create the forest plot)

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

In conclusion, this study concludes that stem cell therapy has shown therapeutic effects on the improvement of motor functions in patients with CP. Stem cell therapy also appears to be safe except for some minor and transient adverse effects. However, the methodologies to standardize the maximum efficacy of stem cell, treatment regimes, therapeutic cell dose, and optimal timing of cells therapy is still unknown. Also, the patient selection for stem cell therapy is important to maintain safety and efficacy. Thus, future clinical trials should have longer follow-up durations and include details of specific criteria such as patient's age groups, gender, the timing of injury, severity, and type of CP. Strictly control the safety of studies by optimizing the route of delivery, type of stem cell, and dose to minimize the adverse effects. This may provide more reliable evidence for future treatment options. In the future, parents of patients who are diagnosed with CP can be given the option of stem cell therapy as a biological intervention to improve their children's motor function.

DISCLOSURE

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Conflict of interest: None

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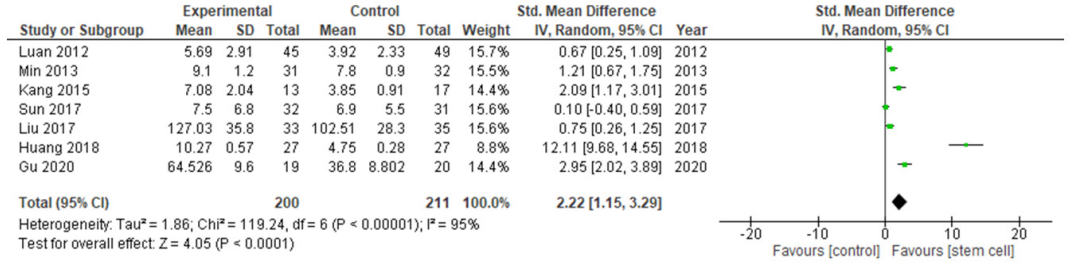
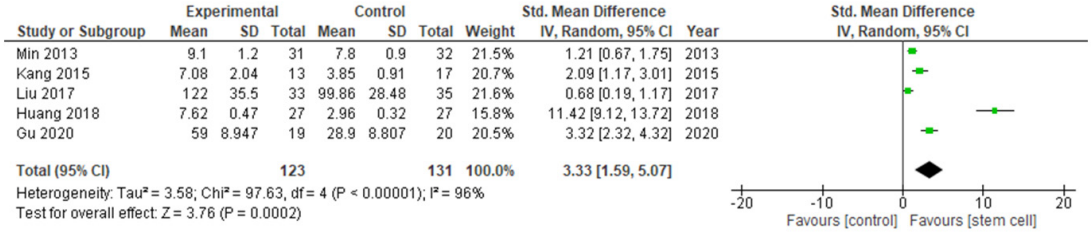
Supplementary



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

Search Terms

MEDLINE PubMed (n=114)
CENTRAL, Cochrane library (n=41)

1. cerebral palsy
2. stem cell
3. amnion epithelial cells
4. hAECs
5. CD34
6. embryonic stem cells
7. ESCs
8. fetal stem cells
9. induced pluripotent stem cells
10. iPSCs
11. mesenchymal stem cells
12. MSCs
13. multipotent adult progenitor cells
14. MAPC
15. neural stem cells
16. NSCs
17. olfactory ensheathing cells
18. oligodendrocyte progenitor cells
19. OPCs
20. Umbilical cord blood
21. UCB
22. hUCBs
23. Motor function
24. Gross motor
25. Physical status
26. Physical disability
27. Physical ability
28. Gross Motor Function Measure
29. Gross motor function
30. OR 2-22
31. OR 23-29
32. #1 AND #30 AND 31

Embase (n=145)
Google scholar (n=6290)

1. Cerebral palsy
2. stem cell
3. umbilical cord blood
4. mesenchymal stem cell
5. neural stem cell
6. embryonic stem cell
7. amnion epithelial cells
8. oligodendrocyte progenitor cell
9. OR 2-8
10. Gross motor function
11. 1 AND 9 AND 10