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A systematic review of cell therapy modalities and outcomes in cerebral palsy

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Abstract

Cerebral palsy is widely recognized as a condition that results in significant physical and cognitive disabilities. Interventions aim to improve the quality of life and reduce disability. Despite numerous treatments and significant advancements, cerebral palsy remains incurable due to its diverse origins. This review evaluated clinical trials, studies, and case reports on various cell therapy approaches for cerebral palsy. It assessed the clinical outcomes of applying different cell types, including mesenchymal stem cells, olfactory ensheathing cells, neural stem/progenitor cells, macrophages, and mononuclear cells derived from peripheral blood, cord blood, and bone marrow. In 60 studies involving 1474 CP patients, six major adverse events (0.41%) and 485 mild adverse events (32.9%) were reported. Favorable therapeutic effects were observed in 54 out of 60 cell therapy trials, indicating a promising potential for cell treatments in cerebral palsy. Intrathecal MSC and BM-MNC applications revealed therapeutic benefits, with MSC studies being generally safer than other cell therapies. However, MSC and BM-MNC trials have shown inconsistent results, with some demonstrating superior efficacy for certain outcomes. Cell dosage, transplantation route, and frequency of administration can affect the efficacy of these therapies. Our findings highlight the promise of cell therapies for improving cerebral palsy treatment and stress the need for ongoing research to refine treatment protocols and enhance safety. To establish conclusive evidence on the comparative effectiveness of various cell types in treating cerebral palsy, randomized, double-blind clinical trials are essential.

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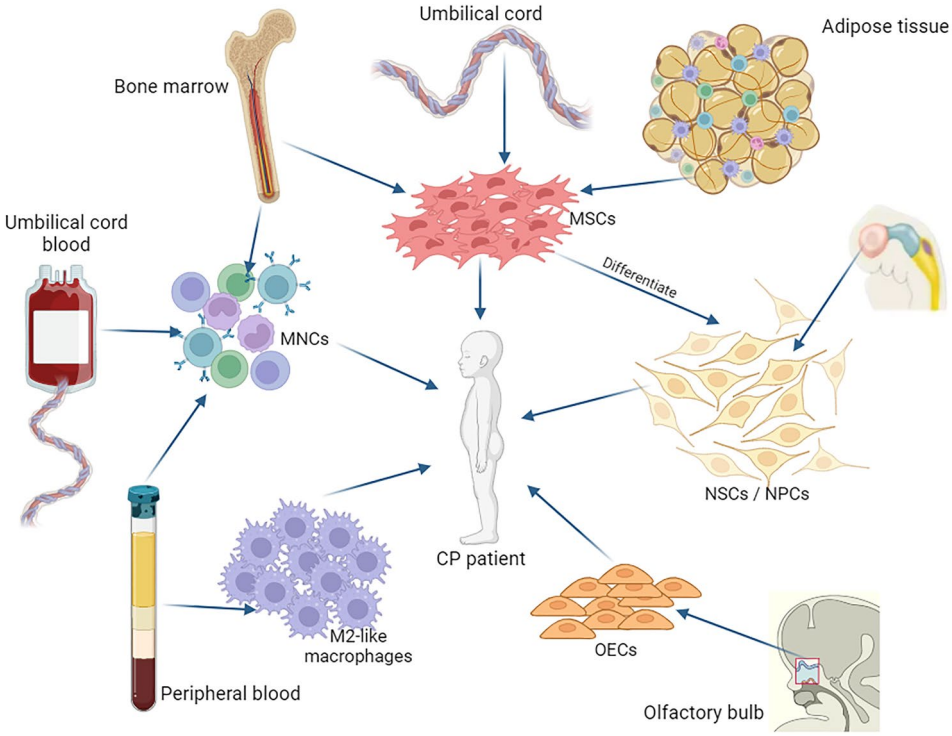
Graphical abstract



Keywords Cerebral palsy · Cell therapy · Clinical trials · Regenerative medicine

Introduction

Cerebral palsy (CP) is widely recognized by health and social service professionals, as well as by a large portion of the general population, as a disorder that causes physical disability. CP has a prevalence of around 2–3 cases per 1000 live births. However, it is considered to be the leading cause of significant physical impairment during infancy. The Surveillance of Cerebral Palsy in Europe (SCPE) group conducted a survey to examine the practices related to CP across the continent and released a set of standardized procedures in 2000 that aim to accurately identify and describe children with CP. This definition had five essential elements: (a) it is an umbrella term; (b) it is persistent but not unchangeable; (c) it involves a disorder of movement and/or posture and motor function; (d) it is caused by a non-progressive interference, lesion, or abnormality; and (e) the immature brain is where the interference, lesion, or abnormality lies [1, 2]. CP is the predominant and most severe motor disability in children. Its severity is evident from the fact that 40% of children with CP lack the ability to walk without assistance, one-third experience epilepsy, up to one-third are unable to speak, and approximately half have varying levels of cognitive impairment [3–8]. CP is a result of atypical development or injury to the brain during the prenatal or neonatal stages. CP resulting from brain insult or damage is characterized as non-progressive or "static" and can manifest throughout the prenatal (congenital brain malformations, intrauterine infections, intrauterine stroke, chromosomal abnormalities), perinatal (hypoxic-ischemic insults, central nervous system infections, stroke, kernicterus), or postnatal (accidental and non-accidental trauma, central nervous system infections, stroke, anoxic insults) stages. The cause of a certain condition in a patient is typically the result of many factors. Prematurity is a significant risk factor for CP, and complications of prematurity that can cause CP include periventricular leukomalacia, intraventricular hemorrhage, and periventricular infarcts [9, 10]. Additional risk factors linked to CP include the presence of multiple pregnancies, restricted development of the fetus inside the womb, maternal drug misuse, preeclampsia (a condition characterized by high blood pressure during pregnancy), chorioamnionitis (inflammation of the fetal membranes), aberrant placental pathology, meconium aspiration (inhalation of the baby's first stool), perinatal hypoglycemia, and genetic vulnerability [10–12]. The management of

CP requires a collaborative approach involving a team of healthcare professionals, such as primary care physicians, neurologists, physiatrists, orthopedists, and other specialists as necessary, depending on any accompanying conditions. Additionally, therapists specializing in physical, occupational, and speech therapy, behavioral health specialists, social workers or case managers, and educational specialists are also involved in the treatment process. Interventions should prioritize the optimization of life quality and the reduction of disability burden. Oral and injectable treatments, such as botulinum toxin, can effectively treat tone irregularities, pain, and concomitant illnesses like epilepsy, sialorrhea, gastrointestinal problems, and behavior disorders. Pharmaceuticals employed to treat spasticity include benzodiazepines, baclofen, dantrolene, tizanidine, cyclobenzaprine, botulinum toxin, and phenol. Clinicians frequently use medications like trihexyphenidyl, gabapentin, carbidopa-levodopa, and benztropine to treat dystonia. The therapy for sialorrhea involves the administration of glycopyrrolate, atropine drops, and scopolamine patches. Anti-convulsant drugs are administered to individuals suffering from epilepsy. CP commonly leads to constipation, which necessitates the use of stool softeners and pro-motility medicines. Anti-inflammatory medications target pain, whereas antidepressants are used to treat sadness and anxiety. Possible surgical interventions include the insertion of a baclofen pump, selective dorsal rhizotomy, tendon releases, hip derotation/rotation surgery, spinal fusion, strabismus correction, and deep brain stimulation [13–15]. Despite the availability of over 180 different therapies and significant advances in the field of prevention, CP remains incurable due to its various causes, including hereditary factors. Although there has been a 30% decrease in the occurrence of CP, a definitive cure has not yet been found [16]. Hence, cell treatment for individuals with CP is not universally applicable. Information is being gathered on the distinct cell types, dosages, timing of therapy, and methods of delivery that might potentially benefit different subgroups [17]. In this review, we have investigated clinical trials, clinical studies and case reports that used different cell therapy strategies for the treatment of CP and reviewed the clinical outcomes of applications of different cell types, including mesenchymal stem/stromal cells (MSCs), olfactory ensheathing cells (OECs), neural stem cells (NSCs), neural progenitor cells (NPCs), macrophages, and peripheral blood (PB), cord blood (CB), and bone marrow (BM) derived mononuclear cells (MNCs), with different routes, timing, and dosages. The findings of these studies suggest that there are a wide range of cell therapy strategies that have shown promise in the treatment of CP. However, further research is still needed to determine the optimal combination of cell type, dosage, timing, and delivery method for different subgroups of patients with CP.

Materials and methods

Eligibility criteria

This comprehensive review encompassed clinical trials, clinical studies, and case reports pertaining to individuals diagnosed with CP. We conducted an in-depth evaluation of several cellular therapy approaches for patients with CP, without imposing any limitations on the timing of injections, delivery modalities, or dose. The review included studies that utilized cellular products both alone or as components of a more intricate therapeutic regimen, case reports, clinical studies and completed clinical trials investigating the efficacy of cell therapy for individuals with CP. The study did not include trials using non-human subjects, qualitative research methods, clinical applications without post-operative quantitative data, and studies with insufficient findings.

Literature search and study selection

A thorough literature search was performed utilizing four databases: PubMed, the U.S. National Library of Medicine (Clinicaltrials.gov), Science Direct, and the Cochrane Library. The search aimed to identify papers released from 2010 until February 2024 as this period marks a crucial milestone in the field. The key legislative changes during this time include the integration of the European Union (EU) Advanced Therapy Medicinal Products (ATMPs) Regulation into national laws and the reinforcement of pharmacovigilance requirements for advanced therapies (Regulation EU No. 1235/2010 and Directive 2010/84/EU). The exclusion criteria for this review consisted of three categories: (a) trials conducted on non-human subjects; (b) reviews and other studies that were not specifically designed as clinical trials or clinical studies or case reports; (c) studies that lacked sufficient quantitative data; and (d) studies that did not have accessible full-length papers that could be retrieved.

Data collection and quality evaluation

The included databases yielded a total of 2515 references, with 73 from Pubmed, 34 from Clinicaltrials.org, 2287 from ScienceDirect, and 121 from the Cochrane Library. After conducting a thorough review of titles and abstracts, a total of 60 studies were found to be suitable for inclusion in this systematic review. These studies were published between 2010 and February 2024 and involved cell therapy clinical trials, clinical studies, or case reports with quantitative results related to the treatment of patients with CP. Table 1

Table 1 List of cell therapy studies that are included in this systematic review for the treatment of CP

No.	Study reference	Study type	Type of cell therapy
1	Sharma et al. (2012) [18]	Clinical study	BM-MNCs
2	Purandere et al. (2012) [19]	Case report	BM-MNCs
3	Mancias-Guerra et al. (2014) [20]	Clinical trial (NCT01019733)	BM-MNCs
4	Sharma et al. (2015)[a] [21]	Case report	BM-MNCs
5	Sharma et al. (2015)[b] [22]	Clinical trial (NCT01978821)	BM-MNCs
6	Bansal et al. (2016) [23]	Clinical study	BM-MNCs
7	Abi Chahine et al. (2016) [24]	Clinical study	BM-MNCs
8	Nguyen et al. (2017) [25]	Clinical trial (NCT02569775)	BM-MNCs
9	Nguyen et al. (2018) [26]	Clinical trial (NCT02574923)	BM-MNCs
10	Thanh et al. (2019) [27]	Clinical trial (NCT03123562)	BM-MNCs
11	Liem et al. (2020) [28]	Case report	BM-MNCs
12	Tarkan et al. (2021) [29]	Clinical study	BM-MNCs
13	Cox et al. (2022) [30]	Clinical trial (NCT01988584)	BM-MNCs vs CB-MNCs
14	Zali et al. (2015) [31]	Clinical trial (NCT01404663)	BM derived CD133 + cells
15	Sun et al. (2010) [32]	Clinical study	CB-MNCs
16	Papadopoulos et al. (2011) [33]	Case report	CB-MNCs
17	Xing et al. (2012) [34]	Clinical study	CB-MNCs
18	Lee et al. (2012) [35]	Clinical study	CB-MNCs
19	Min et al. (2013) [36]	Clinical trial (NCT01193660)	CB-MNCs
20	Feng et al. (2015) [37]	Clinical study	CB-MNCs
21	Kang et al. (2015) [38]	Clinical trial (NCT01528436)	CB-MNCs
22	Romanov et al. (2015) [39]	Clinical study	CB-MNCs
23	Jensen et al. (2016) [40]	Case report	CB-MNCs
24	Sun et al. (2015) [41]	Clinical trial (NCT01147653)	CB-MNCs
25	Sun et al. (2017) [42]	Clinical trial (NCT01147653)	CB-MNCs
26	Min et al. (2020) [43]	Clinical trial (NCT01991145)	CB-MNCs
27	Tsuji et al. (2020) [44]	Clinical trial (NCT02256618)	CB-MNCs
28	Sun et al. (2021) [45]	Clinical trial (NCT02599207)	CB-MNCs
29	Huang et al. (2021) [46]	Clinical study	CB-MNCs
30	Kikuchi et al. (2022) [47]	Clinical trial (Japan Registry of Clinical Trials—jRCTb060190039)	CB-MNCs
31	Zarabi et al. (2022) [48]	Clinical trial (NCT03795974)	CB-MNCs
32	Crompton et al. (2020) [49]	Clinical trial (NCT03087110)	CB-MNCs
33	Crompton et al. (2022) [50]	Clinical trial (NCT03087110)	CB-MNCs
34	Rah et al. (2017) [51]	Clinical study	PB-MNCs
35	Koh et al. (2018) [52]	Clinical study	PB-MNCs
36	Li et al. (2012) [53]	Case report	MSCs
37	Hassan et al. (2012) [54]	Clinical study	MSCs
38	Wang et al. (2013) [55]	Case report	MSCs
39	Wang et al. (2013) [56]	Clinical study	MSCs
40	Ren et al. (2013) [57]	Clinical study	MSCs
41	Wang et al. (2015) [58]	Clinical study	MSCs
42	Zhang et al. (2015) [59]	Case report	MSCs
43	Miao et al. (2015) [60]	Clinical study	MSCs
44	Liu et al. (2017) [61]	Clinical study	MSCs vs BM-MNCs
45	Dong et al. (2018) [62]	Case report	MSCs
46	Okur et al. (2018) [63]	Case report	MSCs
47	Kabataş et al. (2018) [64]	Case report	MSCs
48	Huang et al. (2018) [65]	Clinical study	MSCs
49	Boruczkowski et al. (2019) [66]	Clinical study	MSCs
50	Fu et al. (2019) [67]	Clinical study	MSCs

Table 1 (continued)

No.	Study reference	Study type	Type of cell therapy
51	Gu et al. (2020) [68]	Clinical trial (Chinese Clinical Trial Register—ChiCTR1800016554)	MSCs
52	Kabataş et al. (2021) [69]	Clinical study	MSCs
53	Amanat et al. (2021) [70]	Clinical trial (NCT03795974)	MSCs
54	Sun et al. (2022) [71]	Clinical trial (NCT03473301)	MSCs vs CB-MNCs
55	Luan et al. (2012) [72]	Clinical study	NPCs
56	Chen et al. (2013) [73]	Clinical trial (Chinese Clinical Trial Register—ChiCTR-TRC-12002056)	NPCs
57	Lv et al. (2023) [74]	Clinical trial (NCT03005249)	NSCs
58	Huang et al. (2009) [75]	Clinical study	OECs
59	Chen et al. (2010) [76]	Clinical study	OECs
60	Chernykh et al. (2014) [77]	Clinical study	M2 like macrophages

BM bone marrow, *CB* cord blood, *MNC* mononuclear cell, *FSC* fetal stem cell, *MSC* mesenchymal stem cell, *NPC* neural progenitor cell, *NSC* neural stem cell, *OEC* olfactory ensheathing cells, *PB* peripheral blood

provides a comprehensive list of 60 studies that are included in this review.

Results

Characteristics of included studies

A total of 60 studies [18–77] that met the criteria for inclusion in the present review were categorized based on the specific kind of cells employed in the treatment of CP (Table 1). Out of these studies, 23 were clinical trials, with 20 of them being registered in the NIH database (ClinicalTrials.gov), two documented in the Chinese Clinical Trial Register, and one registered in the Japan Registry of Clinical Trials. Out of the total number of papers included, 26 were clinical studies and 11 were case reports (which were not registered in clinical trial databases but authorized by particular ethics committees).

Cell therapy strategies for the treatment of CP

A total of 14 studies examined the safety and effectiveness of BM-MNCs applications [18–31]. One study compared the efficacy of BM- and CB-MNCs [30], while another study focused on BM-derived CD133+ cells [31]. Furthermore, 19 studies investigated CB-MNCs therapy in the treatment of CP [32–50] and two studies investigated the use of MNCs derived from PB [51, 52]. In addition, 19 studies were conducted to assess the safety and efficacy of MSC therapy [53–71]. Among these, one study compared MSC and CB-MNC applications [71], and another study compared the efficacy of MSCs and BM-MNCs [61]. Moreover, two studies were carried out using neural progenitor cells (NPCs) [72, 73], one trial utilized NSCs [74], and two studies employed olfactory ensheathing cells [75, 76], and lastly, one study focused on the use of M2-like macrophages [77]. Table 1 provides a comprehensive overview of the different study types and corresponding cell treatment types used in the aforementioned investigations. It is worth noting that these studies demonstrate the diverse range of cell therapies being explored in the field of regenerative medicine, highlighting the potential for novel and innovative approaches to treating CP.

Bone marrow-derived mononuclear cells

A BM-MNC product is typically a cell cocktail isolated from autologous bone marrow via density gradient separation steps that can be applied to the patient right after the isolation process or cryopreserved for future use. A typical BM-MNC product consists of lymphocytes, monocytes, hematopoietic stem/progenitor cells, endothelial stem cells, and MSCs. The ratio and amount of these cells may vary according to the volume of the bone marrow tissue processed, the patient's age, and their condition. It is reported in the literature that BM-MNCs can work through multiple mechanisms, including neuroprotection, immunomodulation, neurorestoration, and neurogenesis, to improve motor and neural function in patients with CP. BM-MNCs create therapeutic effects by releasing vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), and insulin-like growth factor 1 (IGF-1), reducing inflammation by releasing interleukin-10 (IL-10), changing the immune response in the damaged brain, encouraging the growth of endogenous neural stem and progenitor cells and helping them differentiate into neurons and oligodendrocytes, improving the production of new neurons from endogenous neural stem cells, helping the brain heal, and encouraging the revascularization and repair of damaged blood vessels in the brain. MSCs in BM-MNCs play a significant role in tissue repair and regeneration, secreting

Table 2 Studies conducted with bone marrow-derived mononuclear cells

Study reference	Number of patients enrolled Tre.	Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Sharma et al. (2012) [18]	20	–	Single intrathecal (L4–L5) administration of 1×10^6/kg autologous BM-MNCs (27×10^6 MNCs avg. per patient)	Improvement observed in 85% of the patients (significant improvement in 15%) Improved motor functions in 3 patients	No major AEs 5 patients (25%) had minor AEs (headache, neck stiffness, vomiting and nausea)	15 ± 1
Purandere et al. (2012) [19]	1	–	5 consecutive intrathecal administrations of a median of 112.28×10^6 (range, $86.9–32.8\times10^6$) autologous BM-MNCs The first 3 doses were given with 7 days intervals, 4th infusion after six months, and 5th infusion after one year	Significant improvement in motor and cognitive functions Improvement in speech	No serious AEs reported	24
Mancias-Guerra et al. (2014) [20]	18	–	Single intrathecal administration of avg. 1312×10^6 (range $483–5387\times10^6$) autologous BM-MNCs including avg. 10.02×10^6 (range $1.02–29.9\times10^6$) CD34 + HSCs Consequent IV infusion of BM aspirate including avg. 6.01×10^8 (range $1.36–17.85\times10^8$) BM-MNCs and 3.39×10^6 (range $1.04–9.4\times10^6$) CD34 + HSCs	Significant improvement observed in BDI scores of personal-social, cognitive, developmental age, adaptive, motor and communication skills in all patients	No major AEs 3 patients (16.7%) had minor AEs (headache, neck stiffness, vomiting and low grade fever)	6
Sharma et al. (2015)[a] [21]	1	–	Single intrathecal (L4-L5) administration of 33×10^6 autologous BM-MNCs	Improvement in trunk strength, upper and lower limb control Improvement in motor functions Improvement observed in brain PET-CT scans	Not reported	6
Sharma et al. (2015)[b] [22]	40	–	Single intrathecal (L4–L5) administration of avg. 10.23×10^6 autologous BM-MNCs	Improvements were observed in 92.5% of the patients, 10 patients (25%) had significant improvement in neuro-evaluations	2 patients experienced major AEs (seizures)	6
Bansal et al. (2016) [23]	10	–	Single intrathecal (L4–L5) administration of avg. 4500×10^6 autologous BM-MNCs	Significant improvement in gross motor functions	No major AEs reported	24
Abi Chahine et al. (2016) [24]	17		Single intrathecal (L4–L5) administration of 2×10^6 autologous BM-MNCs/kg body weight	Significant improvement in gross motor functions in 73% of the patients Improvement in spasticity and cognitive function in 40% of the patients	No major AEs 5 patients (29.4%) had minor AEs (headache, fever and vomiting)	Not specified
Nguyen et al. (2017) [25]	40	–	2 intrathecal (L4–L5) administrations with 3 months intervals 27.2×10^6 autologous BM-MNCs (including 2.6×10^6 CD34 + HSCs)/kg body weight for the 1st administration and 17.1×10^6 BM-MNCs (including 1.7×10^6 CD34 + HSCs)/kg body weight for the 2nd administration	Significant improvement in gross motor functions Significant reduction in muscle spasticity	No major AEs 21 patients had minor AEs, fever (30%) and vomiting (22.5%)	6
Nguyen et al. (2018) [26]	30	–	2 intrathecal (L4–L5) administrations of autologous BM-MNCs with 3 months intervals Cell dosage of BM-MNC product was not specified	Significant improvement in gross motor functions Significant reduction in muscle spasticity Significant increase in quality of life scores	No major AEs reported	6

Table 2 (continued)

Study reference	Number of patients enrolled Tre.	Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Thanh et al. (2019) [27]	25	–	2 intrathecal (L4–L5) administrations of autologous BM-MNCs with 6 months intervals The average numbers of BM-MNCs were $17.4 \pm 11.9 \times 10^6$/kg including $1.5 \pm 1.4 \times 10^6$/kg CD34 + cells, for the first transplantation $15.0 \pm 12.8 \times 10^6$/kg BM-MNCs including $1.1 \pm 1.1 \times 10^6$/kg CD34 + cells for the second transplantation	Significant improvement in gross motor functions Significant reduction in muscle tone	No major AEs occurred. Minor AEs included vomiting (32%), local pain (16%), and mild fever without any identified infection (4%)	12
Liem et al. (2020) [28]	30	–	2 intrathecal (L4–L5) administrations with 3 months intervals Cell dosage of autologous BM-MNC product was not specified	Significant improvement in gross motor functions Significant reduction in muscle spasticity	No major AEs reported	6
Tarkan et al. (2021) [29]	20	–	Single intrathecal (L4–L5) administration Cell dosage of autologous BM-MNC product was not specified	Significant improvement in gross motor functions	Not reported	12
Cox et al. (2022) [30]	13	7	Single IV infusion of autologous BM-MNCs (10 patients) or autologous CB-MNCs (3 patients) or placebo (7 patients) 6×10^6 cells/kg body weight	Significant improvement in corticospinal tract radial diffusivity	No major AEs reported related to the therapy	24
Zali et al. (2015) [31]	12	–	Single intrathecal (L4–L5) administration of an average of 10.8×10^6 (range $45–176 \times 10^6$) autologous CD133 + enriched BM-MNCs	Significant improvement in gross motor functions Reduction in the severity of spasticity Improvement in posture and contracture deformities	No major AEs 5 patients (41.6%) had minor AEs (headache, nausea, vomiting)	6

AE adverse events, *BDI* battelle development inventory, *BM* bone marrow, *HSC* hematopoietic stem cell, *IV* intravenous, *MNC* mono nuclear cell

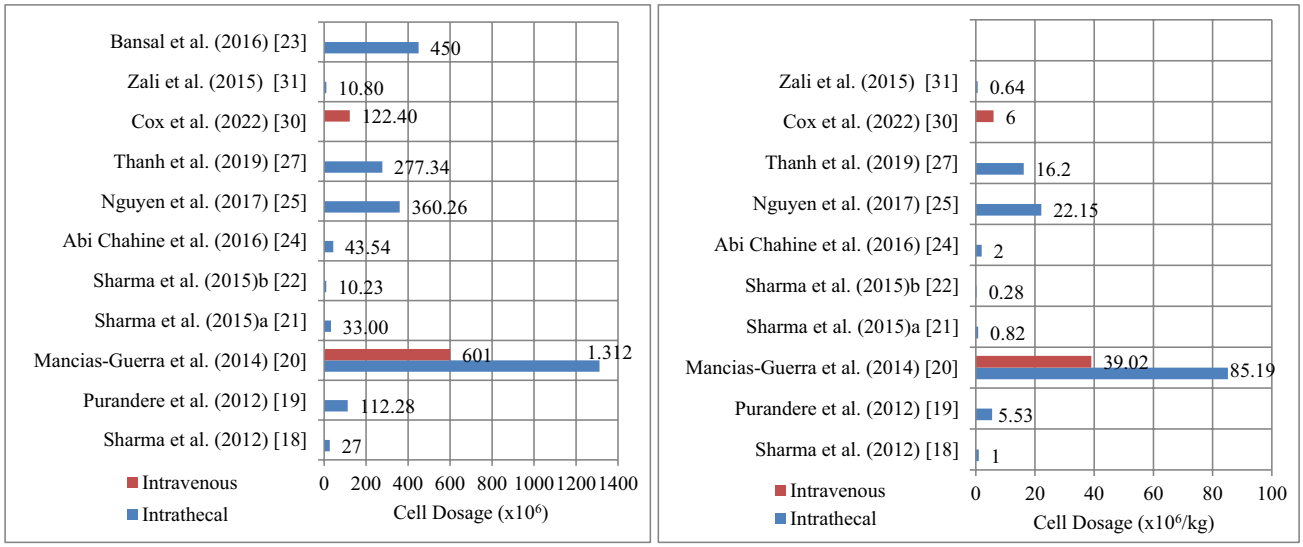
growth factors and cytokines that aid in healing and anti-inflammatory processes [78–80]

Upon careful examination of 14 studies involving BM-MNCs [18–31] (Table 2), it is noticeable that out of 277 patients who had BM-MNC treatments, only 2 patients (0.73%) encountered serious AEs (seizures), both of which occurred within the same research group. A total of 126 minor AEs were reported among all BM-MNC studies which were temporary and eliminated with appropriate treatments. The most frequently occurring mild AEs were vomiting ($n = 43$, 15.69%), headache ($n = 20$, 7.29%), and pain at the administration site ($n = 20$, 7.29%). The occurrence of typical side effects such as headache and nausea may be attributed to the increase in intracranial pressure during intrathecal administrations. Additionally, incidences of low-grade fever might be a result of the immune reaction against the application of cell therapy, given the nature of the treatment (Table 2). All research included in this review [18–29, 31] administered BM-MNCs through the intrathecal route, with the exception of one study [30] that used the IV method. The purpose of this particular study was to compare the effects of IV infusions of BM-MNCs and CB-MNCs for the treatment of CP. Out of the 14 trials, seven used a single administration [18, 20–24, 29, 31], four used double applications [25–28], one used five consecutive intrathecal administrations [19], and one study utilized combined application of intrathecal and IV administrations [20]. The BM-MNC dosage varied excessively among these studies. The computed median cell dosage used was 250.8×10^6 BM-MNCs. However, there was substantial variability in doses, with the lowest dose being 10.23×10^6 [22] and the highest dose being 1312×10^6 [20]. The average cell dose in studies that did not provide the average weight of the patients enrolled, was determined based on the average weight/age data of children as given by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) [81–83]. Table 3 displays a graph illustrating the doses of BM-MNC utilized in the aforementioned studies. Every study examining the motor abilities of individuals with CP reported notable enhancements in their overall motor functioning, as well as a decrease in muscular stiffness and spasticity. These gains were measured using the gross motor function classification system (GMFCS), the Ashworth Scale, and the Gross Motor Function Measure (GMFM-66 and GMFM-88) scores [19, 23–31]. All research utilizing alternative assessment techniques such as the Functional Independence Measure (FIM), Vineland Adaptive Behavior Scale (VIMS), the Battelle Developmental Inventory (BDI), MRI and PET-CT brain imaging [18–22, 26, 30, 31] has indicated notable enhancements in quality of life (QoL), cognitive abilities, and neurological functioning. A study that used a slightly different cell therapy product and increased the number of CD133+ cells in BM-MNCs [31] also found significant improvements in posture, gross motor skills, and deformities caused by contractures. Additionally, there was a reduction in the degree of spasticity, and no significant adverse events were observed. These findings suggest that intrathecal administration of BM-MNCs may have a broad range of positive effects on various aspects of physical and cognitive functioning in individuals with CP. Further research is needed to fully understand the mechanisms underlying these improvements and to optimize the use of cell therapy in clinical practice.

Cord blood mononuclear cells

A CB-MNC product is also a heterogeneous cell therapy product isolated from CB via density gradient separation steps and cryopreserved for future clinical applications. Considering the collection time of the cord blood is always during delivery, the CB-MNC product is always cryopreserved and thawed before use in an autologous setting. CB-MNCs have a higher proportion of HSCs compared to BM, which are essential for the formation of various blood cells. MSCs are present in smaller quantities in CB compared to BM. However, CB is enriched with naïve T cells, which can be advantageous in the regulation of the immune system [84, 85]. CB-MNCs possess potent anti-inflammatory characteristics, making them essential in the management of CP, where inflammation plays an important part in the development of the condition. These cells release various anti-inflammatory cytokines, including IL-10 and transforming growth factor beta (TGF-β). These cytokines aid in the reduction of brain inflammation, therefore protecting neurons from inflammatory damage. CB-MNCs have the ability to regulate the immune response, hence decreasing the immunological-related damage frequently observed in CP. The presence of naive T cells in CB-MNCs regulates the immune response, lowering the risk of inflammation-related brain damage. This immunomodulatory action facilitates the development of a more conducive environment for brain repair and regeneration. Neurotrophic factors, such as BDNF and glial cell line derived neurotrophic factor (GDNF), are released by CB-MNCs and help neurons survive, grow, and be active. These factors help protect existing neurons by stopping apoptosis and encouraging the regeneration of damaged neural tissues. CB-MNCs stimulate tangiogenesis and neurogenesis, which are essential processes for repairing and recovering the brain in CP. CB-MNCs secrete VEGF and angiopoietin-1 (Ang-1), which stimulate the development of new blood vessels in the brain. Enhanced blood circulation promotes the transportation of oxygen and nutrients to the affected regions, facilitating the restoration of brain tissue and an improvement in functionality. Moreover, these

Table 3 Cell dosages used in BM-MNC studies



(A) The graph for the average total number of cells ($\times 10^6$) applied in BM-MNC studies; (B) The graph for the average number of cells per body weight ($\times 10^6$/kg) applied in BM-MNC studies

Studies that did not provide information on the quantity of BM-MNCs utilized [26, 28, 29] were excluded in the graphs. One study [23] was excluded from graph B due to unattainable patient weight data

cells facilitate the generation of fresh neurons and glial cells, thus assisting in the regeneration of impaired brain tissue [84, 85]

A total of 17 clinical studies have been carried out with CB-MNCs for the treatment of CP since 2010 [32–50] and a total of 578 CP patients have received CB-MNC therapy during these studies (Table 4). Although a total of 21 major AEs in the treatment groups (3.56%) were reported, only 3 (0.5%) of them (hypertension, acute wheeze and hypokalemia) were reported to be related with the intervention. A total of 266 minor AEs reported to be experienced by patients. Most common minor AEs occurred were upper respiratory infection (9.68%), fever (7.78%) and nausea (5.36%) (Supplementary Table 1). Because headache and nausea AEs were only reported in studies that used intrathecal route for administration, it can be suggested that these AEs may be linked to an increase of intracranial pressure during administrations.

Administration routes and number of applications preferred in these studies were; a single IV infusion in 12 studies [32, 33, 35, 36, 38, 40–43, 45–47, 49, 50], multiple IV infusions in two studies [39, 44], a single intrathecal administration in one study [48], and combined IV + intrathecal administrations in two studies [34, 37]. The CB-MNC doses delivered in each study exhibited significant variations, ranging from a minimum dosage of 25×10^6 [37] to a maximum dosage of 840×10^6 [34], given in a single infusion and when the cell dosage is evaluated according to the patient's body weight, the lowest dosage was 1.23×10^6/kg [37] and the highest dosage was 52.27×10^6/kg [38]. The mean number of CB-MNCs employed throughout all studies included in this review has been calculated to be 338.83×10^6 CB-MNCs or 23.77×10^6/kg for a single administration. The cell dosage has been determined in many studies by the number of cells administered per kilogram of body weight. The mean cell dosage in studies [35, 41, 42, 44–46, 49] did not provide the weight information of the participants was calculated using the mean weight/age data of children provided by the WHO and CDC [81–83]. Table 5 displays the quantities of cells administered in CB-MNC studies included in this review.

Among the 17 clinical studies utilizing CB-MNCs included in this review, 5 of them reported significant improvement, particularly in the motor capabilities of the patients enrolled [33, 34, 36, 38, 48]. Statistical significance of clinical improvement was evaluated compared to a control group in four of these studies. While 9 more studies documented clinical improvements in gross motor skills, muscular tone, cognitive abilities, and mental functions, the outcomes did not demonstrate enough distinction to achieve statistical significance [35, 39, 40, 43, 45–47, 49, 50]. Only one study yielded no evidence of improvement in the treatment group as compared to a control group. However, this study also revealed a notable disparity in the improvements of motor function between patients who were administered a low dosage ($< 20 \times 10^6$/kg) and those who got a large dose ($> 20 \times 10^6$/kg) of CB-MNCs, with the latter group experiencing more favorable outcomes [41, 42]. Finally, three studies concluded their studies without reporting any additional

information about the efficacy of utilizing CB-MNCs in the treatment of CP. However, they did assess the safety and feasibility of CB-MNC therapy approach, also emphasizing the significance of the quality of the processed cell therapy product used [32, 37, 44].

Improvements in motor functions were assessed according to Gross Motor Performance Measure (GMPM), GMFCS, GMFM-66, Modified Ashworth Scale (MAS), the Pediatric Evaluation of Disability Inventory (PEDI), Peabody Gross Motor Quotient, Peabody Fine Motor Quotient, Peabody Developmental Motor Scales (PDMS), Beery-Buktenica Developmental Test of Visual-Motor Integration, Assisting Hand Assessment Interval Score, Quality of Upper Extremity Skills Test (QUEST) and CP Quality of Life (CP-QoL) evaluations among studies included in this review. Additionally, improvements in cognitive functions and neurodevelopment were evaluated according to age-appropriate cognitive assessments, Bayley Scales, Wechsler Preschool Primary Scale of Intelligence (WPPSI-IV), Wechsler Intelligence Scale for Children (WISC), Behavior Rating Inventory of Executive Function (BRIEF), the Strengths and Difficulties Questionnaire (SDQ), Kyoto Scale of Psychological Development (K-test), Denver Development Screening Test and brain MRIs. An overview of clinical outcomes of these studies is presented in Table 4.

Peripheral blood mononuclear cells

There were two studies that used autologous MNCs derived from peripheral blood after granulocyte-colony-stimulating factor (G-CSF) infusion [51, 52]. Among the participants who enrolled in these studies, 7 out of 53 (13.2%) patients were reported to experience mild AEs, whereas no serious AEs were detected. While a study showed that 20 individuals (42.6%) experienced an improvement in neurodevelopmental assessments, there was no definitive meaningful change observed following a single intravenous infusion of 597×10^6/kg PB-MNCs [51]. These findings suggest that the use of autologous PB-MNCs after G-CSF administration may be safe, with only mild AEs reported. However, the efficacy of this treatment in improving neurodevelopmental assessments remains inconclusive based on the results of a single intravenous infusion. An overall summary of these two studies is given in Table 6.

Mesenchymal stem/stromal cells

Unlike MNC products, MSCs are homogenous products that are only composed of one type of cell, which are obtained by proliferating MSCs via cell culture methods. As their production processes can be controlled in-process, the final product can be prepared exactly according to the patient's needs (cell dosage and volume). As they can be used allogenically, there is no need for any intervention for tissue collection from the patient or time for production processes; mass produced and cryopreserved UC-MSCs can be used whenever needed after thawing and quality control processes. MSCs exhibit potent anti-inflammatory characteristics. They release a range of cytokines and growth factors that aid in decreasing inflammation in the brain, including the important anti-inflammatory factors IL-10 and TGF-β. MSCs have the ability to regulate the immune system, hence decreasing the intensity of immunological reactions that play a role in causing brain injury in CP. This is achieved by stimulating the production of regulatory T cells (Tregs) and inhibiting the function of pro-inflammatory cells such as Th17 cells and macrophages, which play a role in the inflammatory response. MSCs release neurotrophic molecules such as BDNF and GDNF, which help neurons survive and function properly. They have the ability to stimulate angiogenesis and neurogenesis by releasing factors such as VEGF, Ang-1, and neurotrophin-3 (NT-3). Furthermore, MSCs have the capacity to migrate to regions of damage or inflammation inside the brain. This innate capacity allows the cells to exert their advantageous effects immediately at the locations of injury. Stromal cell-derived factor-1 (SDF-1) is one of the signals that damaged tissues emit that attracts MSCs. Since the improvement of motor function depends on the brain's ability to adapt and make up for damaged areas, MSCs can also increase neuronal plasticity, a crucial component in CP [68, 86–88].

Of the cell therapy studies included in this review, 19 of them utilized MSCs [53–71] (Table 7). A total of 376 patients took part in these clinical studies and received MSC therapy products. Only one significant AE was observed (0.26%) which was diagnosed as a worsening in epilepsy [66]. However, an overall total of 73 minor AEs were encountered. The most prevalent AEs identified in multiple studies were fever (6.38%), headaches (5.31%), and wound pain at the administration site (4.78%). The other AEs, which were only documented in individual studies, were upper respiratory tract infection, agitation, diarrhea, vomiting, anorexia, constipation, dyspnea, cough, and tachycardia (Supplementary Table 2). Starting from 2015, all 13 studies utilized allogeneic MSCs derived from umbilical cords (Wharton's jelly), with one exception, which was a study to compare BM-MNCs and BM-MSCs in 2017 [61]. Before 2015, all studies [53, 54, 56, 57] used autologous BM-MSCs, except one study in 2013 [55] which was the first clinical application of UC-MSCs for the treatment of CP to our knowledge.

Like other cell therapy products reviewed in this study, there was notable diversity in the cell quantities, frequency of administration, and favored administration techniques for MSC studies. The range of cell dosages used in IV infusions varied from 4×10^6 MSCs [53] to 70×10^6 MSCs

Table 4 Studies conducted with cord blood derived mononuclear cells

Study reference	Number of patients enrolled Tre.	Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Sun et al. (2010) [32]	184	–	IV infusion of a median of 20×10^6/kg (range, 1–133×10^6/kg) autologous CB-MNCs including 0.7×10^5/kg (range, 0.04–6.4×10^5/kg) CD34 + cells	In order to increase the probability of a certain cord blood unit to be appropriate for utilization, it is necessary to gather, manufacture, and preserve a high-quality product	No AEs reported	12
Papadopoulos et al. (2011) [33]	2	–	A single IV infusion of 662×10^6 and 508×10^6 autologous CB-MNCs to two patients, respectively followed by G-CSF administration	Significant motor improvement	No major AEs reported	28
Xing et al. (2012) [34]	30	60[a]	Single intrathecal administration of 300–1000×10^6 allogeneic CB-MNCs followed by a single IV infusion of 300×10^6–1000×10^6 allogeneic CB-MNCs after 1 week	Gross motor functions were significantly improved for lying, turning and sitting scores	No major AEs reported Minor AEs (fever, pain) experienced by some patients (number not specified)	3
Lee et al. (2012) [35]	20	–	A single IV infusion of an average of 55×10^6/kg (range, 6–156×10^6/kg) autologous CB-MNCs	Partial improvement in neurodevelopmental evaluations in 25% of the patients	No major AEs reported 5 patients experienced minor AEs (nausea, hemoglobinuria, urticaria)	6
Min et al. (2013) [36]	35	70[b]	2 injections of rhEPO (500 IU/kg) with 10 h interval followed by a single IV infusion of 30×10^6/kg allogeneic CB-MNCs. Following the cell treatment, patients were administered rhEPO injections at a dosage of 250 IU/kg twice a week for 4 weeks	Significant improvement in gross motor and cognitive functions Enhanced metabolism in the basal ganglia and the thalamus	3 serious AEs (1 pneumonia, 1 influenza, 1 death) in the cell therapy group and 6 in control groups	6
Feng et al. (2015) [37]	47	–	4–8 administrations with 3–5 days intervals depending on the patients' health conditions First applications were IV, and the rest were intrathecal administrations 20–30×10^6 allogeneic CB-MNCs per injection	Allogeneic CB-MNC therapy for patients with severe CP is relatively safe Intrathecal infusion and ages at the initiation of treatment ($\leq$10 years old) might be associated with the occurrence of the adverse events	No serious AEs reported A total of 42 minor AEs occurred. Most commons; fever (20), vomiting (10), seizure (3), headache (3)	6
Kang et al. (2015) [38]	18	18	A single IV or intra-arterial administration of $\geq20\times10^6$ CB-MNCs (avg. 54.6×10^6)	Significant improvement in motor functions	No serious AEs occurred	6

Table 4 (continued)

Study reference	Number of patients enrolled Tre.	Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Romanov et al. (2015) [39]	80	–	2 IV infusions of avg. 250×10^6 CB-MNCs with 2–3 weeks intervals. 55 patients had 2 additional IV infusions	Improvement observed in 69.1% of the patients Improvement in cognitive functions in 52.7% of the patients Both physical and mental improvement was observed in 41.8% The significance of the effectiveness was correlated with the number of cell infusions	No AEs occurred	3–36
Jensen et al. (2016) [40]	1	–	A single IV infusion of 253×10^6 autologous CB-MNCs including 25.3×10^5 CD34 + cells	Improvement in gross motor and cognitive functions	No AEs reported	57
Sun et al. (2015) [41], Sun et al. (2017) [42]	32	31[c]	A single IV infusion of a median of 20×10^6 autologous CB-MNCs/kg (range $3.8–50.3\times10^6$/kg) were administered including a CD34 + cell dose of 0.5×10^5/kg (range $0.05–4.9\times10^5$/kg)	No significant difference in motor functions between placebo and treated groups. But patients who received $>20\times10^6$/kg cell doses showed significant improvement in brain connectivity and motor function compared to those who received $<20\times10^6$/kg cell doses	No serious AEs reported. Only 1 patient experienced fever during both cell and placebo infusions	24
Min et al. (2020) [43]	46[d]	42[d]	A single IV infusion of $>30\times10^6$/kg allogeneic CB-MNCs + 500 IU/kg EPO	Improvement in motor function Improvement in the integrity of the white matter tract including myelination Increasing the cell dose and histocompatibility were associated with improved efficacy	11 serious AEs were reported, 4 of them (pneumonia, seizure, otitis media acute, pyrexia) occurred in the treatment group but they were reported to be unlikely related to the intervention	12
Tsuji et al. (2020) [44]	6	–	Three IV infusions of a total of $240–1400\times10^6$ autologous CB-MNCs including $3–97\times10^5$ CD34 + cells with 24 h intervals	The feasibility and safety of IV transfusion of autologous CB-MNCs was shown	No AEs reported	18
Sun et al. (2021) [45]	15	–	A single IV infusion of a median of 33×10^6/kg (range $18–52\times10^6$/kg) allogeneic CB-MNCs including a median of 0.6×10^5/kg (range $0.1–1.8\times10^5$/kg) CD34 + cells	Improvement in gross motor functions	No AEs related to the cell therapy occurred. 49 AEs (10 serious) reported in 14 participants	24

Table 4 (continued)

Study reference	Number of patients enrolled Tre.	Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Zhang et al. (2021) [46]	8	–	A single IV infusion of a median of 26.3×10^6/kg (range 7.5–48.3×10^6/kg) autologous CB-MNCs	Improvement in motor functions Significant increase in diamagnetism which suggests that increased myelination potentially contributed to the increase of motor connectivity and motor function	No AEs reported	12
Kikuchi et al. (2022) [47]	6	–	A single IV infusion of a median of 8.8×10^6/kg (range 0.29–25×10^6/kg) allogeneic CB-MNCs including a median of 1.8×10^5/kg (range 0.33–6×10^5/kg) CD34 + cells	Improvement in gross motor functions 50% of the participants also showed improvement in language-social scores	No serious AEs occurred	36
Zarabi et al. (2022) [48]	36	36	A single intrathecal administration of 5×10^6/kg allogeneic CB-MNCs	Significant improvement in gross motor functions, muscle tone and self-care scores Significant increase in fractional anisotropy	No serious AEs occurred. 30 minor AEs (low back pain and headache were most common) observed in 17 patients in the treatment group	12
Crompton et al. (2020) [49], Crompton et al. (2022) [50]	12	–	A single IV infusion of a median of 27×10^6/kg (range 8–76×10^6/kg) allogeneic CB-MNCs	Only 3 participants showed improvement in motor functions	A total of 27 AEs (4 of them were serious) occurred in 9 patients. 3 AEs (hypertension, acute wheeze and hypokalemia) were reported to be related to the study	12

AE adverse events, *CB* cord blood, *IV* intravenous, *MNC* mono nuclear cell, *rhEPO* recombinant human erythropoietin

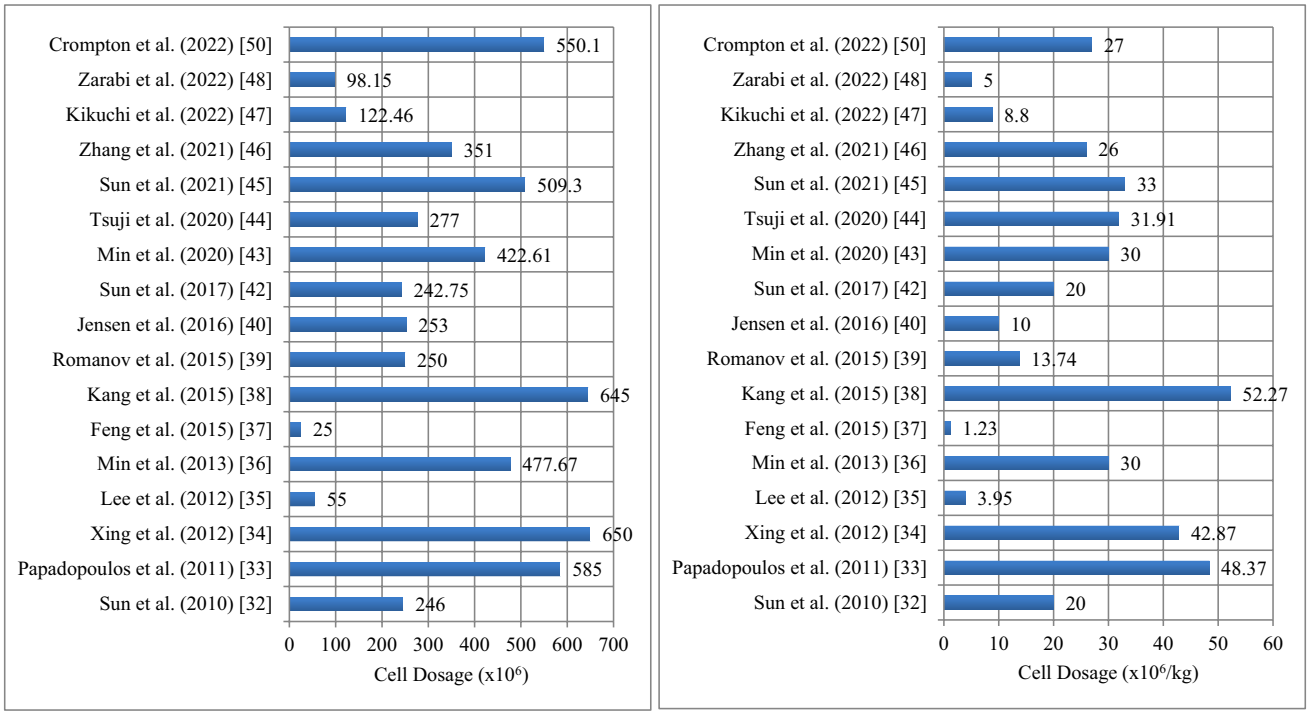
[a]60 CP patients who did not receive cell therapy was divided into two groups, one group receiving mouse neural growth factor + physical rehabilitation therapy (routine treatment), while the other group had no effective treatment

[b]A total of 70 CP patients who did not undergo cell treatment were separated into two groups. One group got recombinant human erythropoietin (rhEPO), placebo CB-MNCs and rehabilitation, while the other group only received rehabilitation

[c]A total of 63 CP patients were enrolled in this study. Patients were randomized to receive an initial infusion of CB-MNCs ($n=32$) or placebo ($n=31$) with a crossover to the alternate infusion 1 year later

[d]While 22 patients in the treatment group received CB-MNCs + EPO, 24 received CB-MNCs + placebo EPO. Also in the control group while 20 patients received placebo CB-MNC + EPO, 22 received placebo CB-MNCs + placebo EPO

Table 5 Graph of average cell dosage used in CB-MNC studies



(A) The graph for the average total number of cells applied in CB-MNC studies; (B) The graph for the average number of cells per body weight ($\times 10^6$/kg) applied in CB-MNC studies

[69], with an average of 28.4×10^6 MSCs. In intrathecal administrations, the lowest cell dosage was 0.76×10^6 MSCs [55], while the highest dosage was 70×10^6 MSCs [69], with an average of 27.04×10^6 MSCs. Regarding cell dosage per body weight, the lowest dosage for IV infusions was 0.28×10^6 MSCs/kg [62], and the highest dosage was 3.14×10^6 MSCs/kg [68] (average of 1.38×10^6/kg). For intrathecal administrations, the lowest dosage was 0.04×10^6 MSCs/kg [55], and the highest dosage was 2×10^6 MSCs/kg [54] (average of 0.94×10^6). Table 8 presents a graph indicating MSC dosages used in all studies included in this review. In two trials, a single IV infusion was used as the treatment regimen [66, 71], but in four other studies, four successive IV infusions were administered with a seven-day gap between each infusion [53, 59, 65, 68]. In two studies [54, 70], a solitary intrathecal administration was done, while the majority of investigations [56–58, 60, 61, 67] involved multiple intrathecal administrations. These studies consisted of 4–6 consecutive applications with intervals ranging from 3 to 14 days. Finally, a total of five studies [55, 62–64, 69] have conducted a combination administration of MSCs by both intrathecal and IV routes.

All 19 MSC utilizing studies included in this review concluded with certain clinical improvement, which is a highly positive outcome. Twelve studies [53, 53, 56, 58, 59, 61, 65–70] found that there was significant improvement in clinical outcomes, particularly in gross motor skills and cognitive capacities. The statistical significance of clinical improvement was assessed by comparing it to a control group in five of these trials [54, 61, 65, 68, 70] and in the remaining studies, the significance was evaluated based on the predicted improvement of a CP patient receiving standard therapy. Evaluations of motor functions were assessed according to GMFCS, GMFM-66, GMFM-88, Fine Motor Function Scale (FMFS), FIM, Manual Ability Classification Scale (MACS), Ashworth Spasm Assessment, MAS, PEDI, Hauser Ambulation Index, PDMS and CP-QoL among studies conducted with MSCs included in this review. Moreover, improvements in cognitive functions and neurological development was evaluated according to Communication Function Classification System (CFSS), Comprehensive Functional Assessment (CFA) scale, CDCC Infant Mental Development Scale, brain MRIs, EEG and computed tomography assessments.

It is also important to clarify that while some MSC studies included in this review referred to the cell therapy product as "mesenchymal stromal cells," these cells are actually classified as MSCs. This is because they have been cultivated for several passages in appropriate cell culture conditions after isolation steps and have undergone tests to ensure certain quality aspects required for clinical use, including flow cytometry analyses, which have demonstrated that these cells express-specific markers associated with MSCs, such as CD44, CD73, CD90, and CD105, while lacking the

expression of markers such as CD34, CD45, CD14, CD31, CD19, CD11b, and HLA-DR [89].

Neural progenitor and stem cells

NSCs and NPCs have the capacity to undergo differentiation into neurons, astrocytes, and oligodendrocytes. This capability is essential for the substitution of missing or damaged cells in the cerebral cortex of individuals with cerebral palsy. They have the ability to differentiate into neurons, which aids in the restoration of neuronal circuits. Astrocytes and oligodendrocytes, on the other hand, provide support and protection to neurons, maintaining optimal brain function. NSCs and NPCs release a range of neurotrophic factors, such as BDNF, GDNF, and nerve growth factor (NGF). These factors promote the survival and proper functioning of neurons that are already present. NSCs and NPCs have the ability to regulate inflammatory conditions within the brain. They release anti-inflammatory cytokines, like IL-10 and TGF-β, that aid in diminishing inflammation and safeguarding neurons against inflammatory harm. The regulation of the inflammatory response is crucial in CP, as inflammation can worsen brain damage. NSCs and NPCs augment neural plasticity, which refers to the brain's capacity to restructure itself through the establishment of novel neural connections. In the context of CP, it is crucial for motor function improvement that the brain can adapt and compensate for regions that have been damaged. NSCs and NPCs can also secrete factors that enhance the ability of synapses to change and make new connections, thereby facilitating the restoration of normal brain function. They release angiogenic molecules such as VEGF, which promote angiogenesis. Enhanced blood circulation to injured regions facilitates the transportation of oxygen and nutrients, hence promoting tissue healing and regeneration. In addition, the recently developed blood vessels facilitate the incorporation and viability of transplanted NSCs and NPCs, as well as the restoration of brain tissues [90–92].

One study utilizing NPCs was included in this review [72]. 45 CP patients received intraventricular administration of $8–10 \times 10^6$ NPCs derived from fetal forebrain tissues and were monitored for 12 months. There were six cases of fever and one case of focal hemorrhage recorded as adverse events. A significant improvement in motor functions compared to a control group was reported after NPC therapy based on GMFM and PDMS assessments. However, this improvement decreased after 3 months post NPC treatment. Another study [73] obtained NSCs by differentiating MSCs derived from autologous BM and succeeded two consecutive intrathecal administrations of $10–20 \times 10^6$ NSC-like cells to 30 CP patients. It was reported in this study that no serious or minor AEs were experienced by any patients. Moreover, a significant improvement in gross motor functions compared to a control group was observed. In a more recent study conducted by Lv et al. [74], 15 CP patients were transplanted with biodegradable gelatin sponge patches, loaded with 5×10^5/kg NSCs, derived from fetal forebrain tissues, into the olfactory fissures of both nasal cavities, three times with 1 month intervals. Two patients went through low-grade

Table 6 Studies conducted with mononuclear cells derived from peripheral blood

Study reference	Number of patients enrolled Tre.	Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Rah et al. (2017) [51]	47	47[a]	G-CSF IV infusion followed by a single IV infusion of 597×10^6/kg PB-MNCs including 3.07×10^6/kg CD34 + cells	20 patients (42.6%) showed overall improvement	No major AEs 7 patients (14.8%) experienced minor AEs	13
Koh et al. (2018) [52]	16	16[b]	G-CSF IV infusion followed by a single IV infusion of PB-MNCs (cell dosage was not specified)	No significant change in cytokine levels No conclusive impact of PBMC reinfusion was observed in this study	Not reported	13

AE adverse events, *Con* control group, *G-CSF* granulocyte-colony-stimulating factor, *IV* intravenous, *MNC* mono nuclear cell, *PB* peripheral blood, *Tre* treatment group

[a]A total of 47 CP patients have completed this trial. During the first month, 28 patients (T1) underwent cell treatment, while 29 patients (T2) were given a placebo. At the seventh month, the groups were switched, with the T1 group receiving a placebo and the T2 group undergoing cell therapy

[b]A total of 16 CP patients have completed this trial. During the first month, 8 patients (T1) underwent cell treatment, while 8 patients (T2) were given a placebo. At the seventh month, the groups were switched, with the T1 group receiving a placebo and the T2 group undergoing cell therapy

Table 7 Studies conducted with mesenchymal stem/stromal cells

Study ref	No. of patients enrolled Tre.	Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Li et al. (2012) [53]	1	–	4 consecutive IV infusions of 40×10^6 autologous BM-MSCs with 7 days intervals	The right lower limb muscle tension was significantly decreased The fundus was slightly wider, and the P100 amplitude (a measure of visual processing in the brain) increased	No AEs occurred	12
Hassan et al. (2012) [54]	26	26	Intrathecal administration of 2×10^6/kg autologous BM-MSCs	Significant improvement in motor functions, independence and communication skills	Not reported	12
Wang et al. (2013) [55]	1	–	7 consecutive combined IV infusions and intrathecal administrations of $5–10\times10^6$ allogeneic UC-MSCs in each session with 1 month intervals. 90% of the cells were IV infused and 10% were injected intrathecally	Improvement in physical strength, adjusted speech and comprehension Reduction in ambulatory	No AEs occurred. Only one episode of temporary fever resolved without any additional treatment	28
Wang et al. (2013) [56]	46	–	For patients who were ≥ 5 years old, 2 intrathecal administrations and 1 intraparenchymal (via stereotactic surgery) transplantation ($n=27$) and for patients who were < 5 years old, 4 intrathecal administrations ($n=19$) of 20×10^6 autologous BM-MSCs with 5 days intervals	Significant improvement in gross motor functions	No major AEs reported. Minor AEs (low fever and wound aches) was observed in a few patients	18
Ren et al. (2013) [57]	2	–	1 patient received 3 intrathecal administrations of a median of 53.1×10^6 autologous BM-MSCs with 7 days intervals Other patient received 4 intrathecal administrations of a median of 49×10^6 autologous BM-MSCs with varying intervals (3–14 days)	Increased muscle strength Reduction in CPSQ scores	No major AEs reported. 1 patient experienced transient fever	24
Wang et al. (2015) [58]	16[a]	–	4 consecutive intrathecal administrations of $40–60\times10^6$ allogeneic UC-MSCs with 3–5 days intervals	Significant improvement in gross motor functions	No AEs occurred	6
Zhang et al. (2015) [59]	1	–	4 consecutive IV infusions of 50×10^6 allogeneic UCB-MSCs with 7 days intervals	Significant improvement in gross motor functions, self-dependence, cognitive ability, and social adaptation	No AEs occurred	60

Table 7 (continued)

Study ref	No. of patients enrolled Tre.	Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Miao et al. (2015) [60]	20	–	4–6 consecutive intrathecal administrations of allogeneic UC-MSCs with 5–7 days intervals. Cell dosage was not specified	12 patients (60%) showed improvement in muscle tone, rigidity and spasm	No major AEs reported. Some patients (≈4 CP patients) experienced transient mild fever, headache and pain	12
Liu et al. (2017) [61]	35[b] 35[b]	35	All patients in the cell therapy group received 4 consecutive intrathecal administrations with 3–4 days intervals 35 patients in the cell therapy group were administered with autologous 1×10^6/kg BM-MSCs and other 35 with BM-MNCs. Patients in control group were rehabilitated with Bobath therapy	Significant improvement in gross motor functions in all patients in the cell therapy group Patients who received MSCs showed better and more persistent improvements compared to those who received MNCs as the follow-up time extended	No major AEs reported. 2 patients in the MSC group experienced mild fever and low intracranial pressure reactions	12
Dong et al. (2018) [62]	1	–	Combined IV infusions and intrathecal administrations of allogeneic UC-MSCs 1st session: 7×10^6 intrathecal + 5.6×10^6 IV; 2nd session: 16.25×10^6 intrathecal + 3.6×10^6 IV; 3rd session: 20.5×10^6 intrathecal	Improvements in EEG, limb strength, motor function, and language expression	Not reported	Not specified
Okur et al. (2018) [63]	1	–	4 consecutive combined IV + intrathecal administrations of 15×10^6 allogeneic UC-MSCs in each application with 2 weeks intervals	Improvement in cognitive skills, trunk control and hand skills	No AEs occurred	12
Kabataş et al. (2018) [64]	1	–	4 consecutive combined IV + intrathecal + intramuscular injections of 1×10^6/kg allogeneic UC-MSCs in each application with 2 weeks intervals	Improvement in cognitive skills, motor functions	No major AEs reported. Only transient early AEs including fever, mild headache, and muscle pain due to injections were reported	12
Huang et al. (2018) [65]	27	27	4 consecutive IV infusions of 50×10^6 allogeneic UCB-MSCs with 7 days intervals	Significant improvement in gross motor and comprehensive functions	No major AEs occurred. A total of 20 minor AEs (upper respiratory tract infection and diarrhea most common) reported in the treatment group	24

Table 7 (continued)

Study ref	No. of patients enrolled Tre.	Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Boruczkowski et al. (2019) [66]	54[c]	–	IV infusion of approximately 1×10^6/kg allogeneic UC-MSCs Number of infusions (1–9) varied according to the clinical status of the patients	48 patients (88.9%) showed improvement in health status and quality of life 21 patients (38.9%) increased their self-service level Significant improvement in muscle tension and strength, gross motor development, communication, attention, social interaction and cognitive function	Only one serious AE occurred, which was epilepsy deterioration	6
Fu et al. (2019) [67]	57	–	4 consecutive intrathecal administrations of 10×10^6 allogeneic UC-MSCs with 5–7 days intervals. After 6 months 27 of these patients received 4 more intrathecal administrations with the same protocol	Significant improvement in motor functions Patients who received 8 administrations showed superior motor function improvement compared to those who received 4	No major AEs occurred. 4 patients experienced headache and 2 patients had transient fever	12
Gu et al. (2020) [68]	20	20	4 consecutive IV infusions of $45–55\times10^6$ allogeneic UC-MSCs with 7 days intervals	Significant improvement in activities of daily living, comprehensive functions and gross motor functions	No major AEs occurred. 3 cases of fever were reported to be related to the cell therapy	12
Kabataş et al. (2021) [69]	8	-	4 consecutive combined IV + intrathecal + intramuscular injections of 1×10^6/kg allogeneic UC-MSCs in each application with 2 weeks intervals	Significant improvement in motor and cognitive scores	No major AEs reported. Only transient AEs including fever, mild headache, and muscle pain due to injections were reported	12
Amanat et al. (2021) [70]	36	36	A single intrathecal administration of 20×10^6 allogeneic UC-MSCs	Significant improvement in gross motor functions Significant increase in self-care, mobility and social function scores Significant increase in fractional anisotropy	No major AEs occurred. The cell treatment group reported a total of 2 cases of fever, 6 cases of agitation, 5 cases of headaches, 8 cases of back pain, and 1 case of vomiting as minor adverse events	12

Table 7 (continued)

Study ref	No. of patients enrolled Tre. Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Sun et al. (2022) [71]	20[d] 25[d] 23[d]	A single IV infusion of 100×10^6/kg allogeneic CB-MNCs for the 1st treatment group ($n=31$) at the baseline. The 2nd treatment group ($n=28$) received 3 consecutive IV infusions of 2×10^6/kg allogeneic UC-MSCs with 3 months intervals. The control group also received a single IV infusion of 100×10^6/kg allogeneic CB-MNCs but 12 months after the first treatment group	Greatest gross motor function improvement was observed in CB-MNC group followed by the UC-MSC group and lowest in the control group at 12th month	There were no significant related AEs. But 8 mild and temporary AEs associated with the cell treatment occurred. These included hypoxia ($n=3$), fever ($n=2$), vomiting ($n=2$), dyspnea ($n=2$), cough ($n=2$), and tachycardia ($n=1$)	24

AE adverse events, *BM* bone marrow, *CPSQ* cerebral palsy survey questionnaire, *IV* intravenous, *MNC* mononuclear cell, *MSC* mesenchymal stem cell, *UC* umbilical cord, *UCB* umbilical cord blood

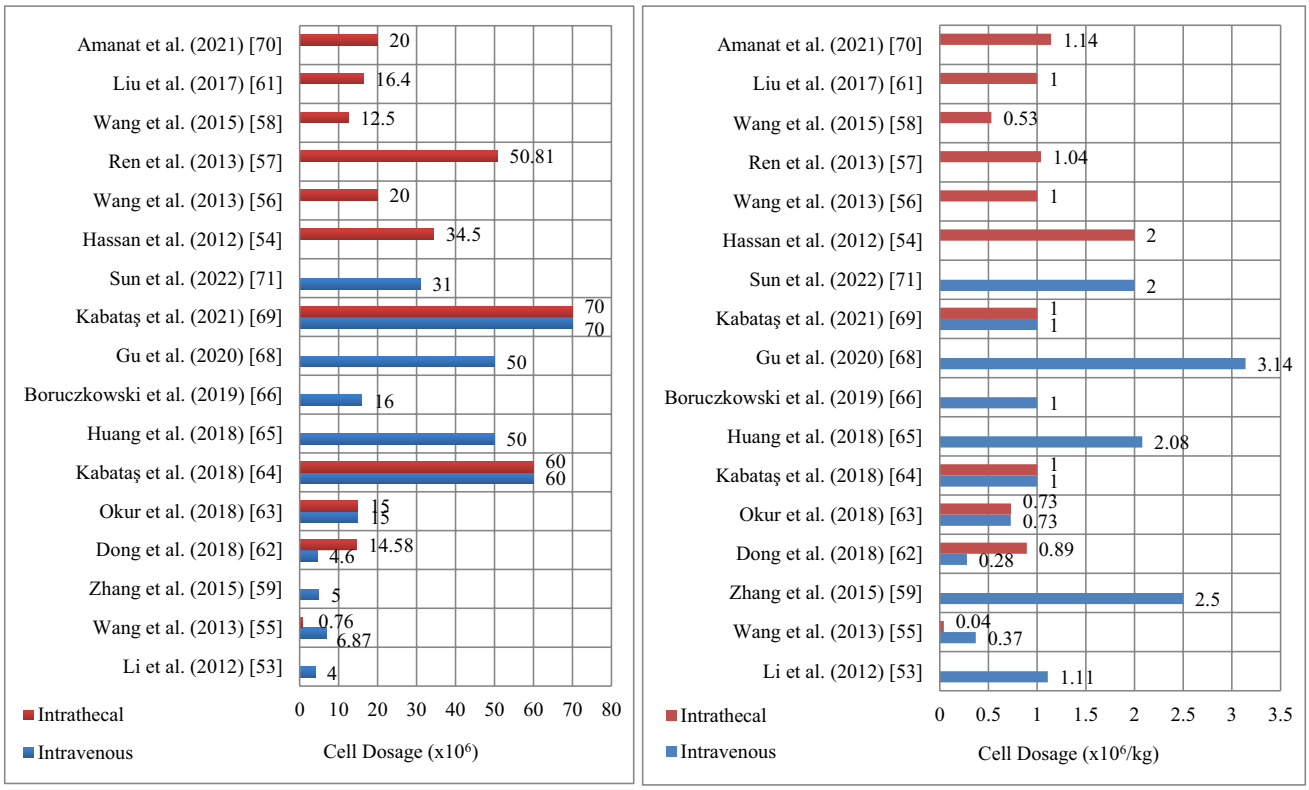
[a]The study population consisted of 8 pairs of identical twins with CP

[b]The treatment group consisted of 70 patients, who were split into two subgroups. In order to compare the effects of BM-MSCs and BM-MNCs, 35 patients were administered BM-MSCs while other 35 patients were administered BM-MNCs

[c]The actual number of patients enrolled in the study for cell therapy was 109, however, 54 patients were able to be followed-up

[d]A total of 59 patients with CP in the treatment group were allocated into two groups in order to assess and evaluate the effectiveness of two distinct cellular products. The initial group ($n=31$) was administered allogeneic CB-MNCs, whereas the second group ($n=28$) was given allogeneic UC-MSCs. 31 CP patients in the control group were administered a cell therapy treatment of allogeneic CB-MNCs after a period of 12 months from the first treatment group. A total of 68 patients (20 in the CB-MNC group, 23 in the UC-MSC group, and 25 in the control group) successfully completed the study analysis

Table 8 Graph of average cell dosages used in MSC studies



(A) The graph for the average total number of cells applied in a single dose in MSC studies; (B) The graph for the average number of cells per body weight ($\times 10^6$/kg) applied as a single dose in MSC studies

fever, one experienced nasal mucosa bleeding, and one had a partial seizure as minor adverse events. No serious adverse events were noted. Patients with CP who received treatment with biodegradable patches containing NSCs demonstrated significant enhancements in gross motor function and self-care skills compared to the control group, as assessed by GMFM-88, FMFS, the Activities of Daily Living (ADL) scale, and Sleep Disturbance Scale for Children SDSC. In total 90 CP patients were treated with NSC/NPCs among studies included in this review. All three studies concluded their study with significant enhancements, particularly in gross motor capabilities, and no occurrences of serious adverse events. This implies a very positive outlook for future research efforts. An overview of NSC/NPC studies and dosage graphs are given in Tables 9, 10.

Olfactory ensheathing cells

OECs have attracted interest due to their potential therapeutic advantages in the treatment of neurological disorders such as CP. OECs are a distinct type of glial cell that is specifically located in the olfactory system. These cells possess the remarkable ability to facilitate the process of repairing and regenerating brain tissue. OECs are recognized for their capacity to facilitate the regrowth of axons. They promote the regeneration of injured axons by establishing a conducive milieu for axonal restoration. OECs provide a range of growth factors and extracellular matrix chemicals that stimulate the development of axons and direct regenerated axons towards their intended destinations. They release neurotrophic factors, including NGF, BDNF, and GDNF. These elements contribute to the viability and operation of neurons, shielding them from programmed cell death and enhancing neural well-being. The neuroprotective effect is essential in cases of cerebral palsy, when the prevention of brain damage is of great importance. OECs demonstrate anti-inflammatory characteristics by regulating the immune response. They have the ability to decrease the activation of microglia and astrocytes, which are commonly implicated in the inflammatory response in the brain. They contribute to brain healing and minimize inflammation-induced neural damage by releasing anti-inflammatory cytokines, such as IL-10 and TGF-β, which produce a more conducive environment. OECs have a significant role in the process of remyelination, which involves the restoration of the protective myelin coating surrounding nerve fibers. This sheath is frequently disrupted in individuals with CP. OECs have the ability to generate myelin and provide assistance to oligodendrocytes, which are the main cells responsible for myelination in the central nervous system. Remyelination

Table 9 Studies conducted with neural progenitor and stem cells

Study reference	Number of patients enrolled Tre.	Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Luan et al. (2012) [72]	45	49	A single intraventricular injection of 8–10 × 10^6 allogeneic NPCs derived from human fetal forebrain tissue	Significant improvement in motor function development. However, the rate of enhancement exhibited a progressive decline following 3 months post NPC application	Hemorrhage in the lobi frontalis cortex on the side of puncture occurred in one patient	12
Chen et al. (2013) [73]	30	30	Two consecutive intrathecal administrations, separated by three weeks, of 10–20 × 10^6 autologous NSC-like cells obtained by differentiating BM-MSCs in vitro	Significant improvement in gross motor functions	No AEs occurred	6
Lv et al. (2023) [74]	15	10	3 consecutive transplantations of patches loaded with 5 × 10^7/kg (about 9.4 × 10^6 NSCs loaded in each patch) allogeneic NSCs onto the olfactory fissure in both cavities, with 1 month intervals	Significant improvement in self-care ability and gross motor functions	No severe AEs related to the treatments occurred. 4 minor AEs (fever, nasal mucosa hemorrhage and CPS) occurred in the treatment group	24

AE adverse events, *BM-MSC* bone marrow-derived mesenchymal stem cells, *CPS* complex partial seizure, *NPC* neural progenitor cell, *NSC* neural stem cell

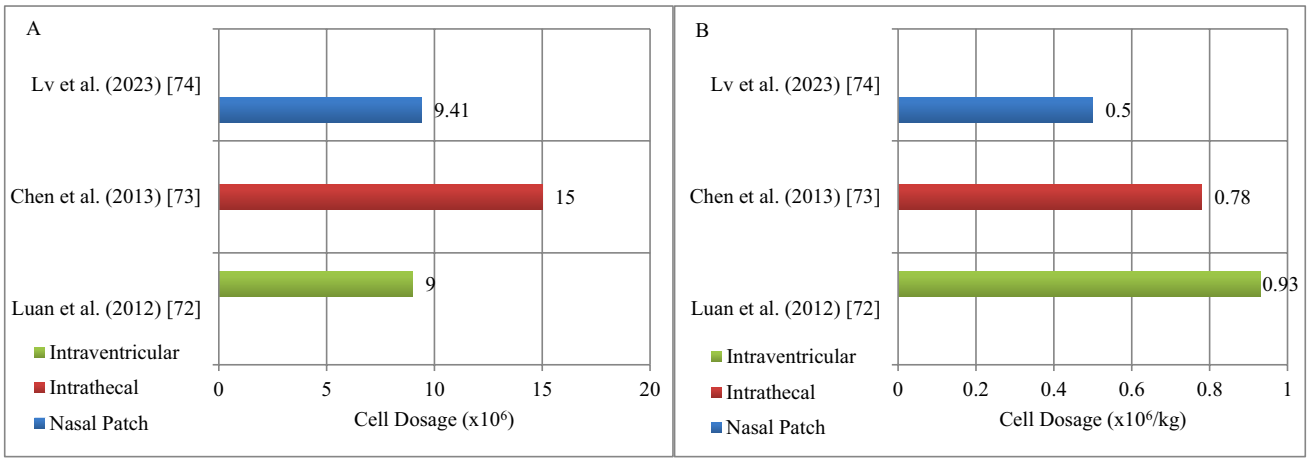
is crucial for reinstating optimal neuronal transmission and enhancing motor function in people with CP. OECs also have the ability to act as a cellular framework, connecting discontinuities in injured brain tissue. They offer essential support for the development of fresh neural connections, making it easier for transplanted cells to be incorporated into the host tissue. The purpose of this scaffold is to preserve the structural integrity of the brain tissue and facilitate functional recovery [93–95].

The initial study [75] employed the application of OECs derived from embryonic olfactory bulbs and included 1255 individuals with different central nervous system disorders had 68 CP patients enrolled in the treatment group. 62 CP patients received an intracerebroventricular injection of 1 × 10^6 OECs derived from human fetal olfactory bulbs in this study. A second therapy method was also involved injecting an additional 1 × 10^6 OECs into the biparietal radial crown lesion, depending on the patient's clinical condition. Patients were monitored for 2–8 weeks (average 4 weeks), and no adverse events were reported for patients with CP, except for two minor adverse events of fever and headache. Based on GMFM assessments, OEC therapy notably enhanced the gross motor skills of 56 (90%) patients with CP. Following this trial, another similar clinical study was performed utilizing OECs derived from embryonic olfactory bulbs [76]. Six CP patients received 2 × 10^6 HLA-DR matching OECs in the frontal lobes utilizing stereotactic methods in this study. They demonstrated enhancements in gross motor and neurological capabilities compared to the control group, with no adverse events reported in the 6-month follow-up period. Based on the results of the previous study [75], the corona radiata of both frontal lobes was chosen as the site for the cell injection. This site was also called "the key point for neural network restoration" in this study [76]. The study concluded that OEC transplantation in the frontal lobes of CP patients led to improvements in motor and neurological functions, supporting the potential of this treatment approach. The choice of the corona radiata as the injection site was based on its significance in neural network restoration, highlighting the importance of precise targeting for optimal outcomes. An overview of these studies is given in Table 11.

M2 like macrophages

M2-like macrophages are a distinct group of macrophages that have a notable impact on tissue regeneration, anti-inflammatory mechanisms, and the control of immune responses. Their therapeutic efficacy for treating CP is becoming increasingly acknowledged owing to their capacity to establish a conducive environment for neuronal restoration and rejuvenation. M2-like macrophages are distinguished by their anti-inflammatory characteristics by

Table 10 Graph of average cell dosages used in NCS and NPC studies



(A) The graph for the average total number of cells applied in a single dose in NCS and NPC studies; (B) The graph for the average number of cells per body weight ($\times 10^6$/kg) applied as a single dose in NCS and NPC studies. The mean cell dosage in studies did not provide the weight information of the participants [72, 73] was calculated using the mean weight/age data of children provided by the WHO and CDC [77–79]

Table 11 Studies conducted with olfactory ensheathing cells

Study reference	Number of patients enrolled Tre.	Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Huang et al. (2009) [75]	62[a]	–	Intracerebroventricular injection of 1×10^6 OECs derived from human fetal olfactory bulbs. Based on the patient's state and MRI results, a biparietal nodal method was also added to inject 1×10^6 OECs into the biparietal radial crown lesion	Improvement in gross motor functions was observed in 90% of the patients	No serious AEs reported. Headache (1 patient) and fever (1 patient) were minor AEs occurred	≈1
Chen et al. (2010) [76]	6	8	2×10^6 OECs derived from human fetal olfactory bulbs were injected into the bilateral corona radiata of the frontal lobes using stereotactic techniques	Improvement in gross motor and neurological functions compared to the control group	No AEs occurred	6

AE adverse events, *OEC* olfactory ensheathing cells

[a]A total of 68 patients were enrolled in the study, 62 of them were able to complete the follow-up

releasing anti-inflammatory cytokines, including IL-10 and TGF-β, that aid in suppressing inflammatory reactions which is vital in cases of CP, as inflammation can worsen neurological damage and hinder the process of rehabilitation. M2-like macrophages regulate the immune response by facilitating a transition from a pro-inflammatory (M1) to an anti-inflammatory (M2) state via hindering the activity of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β), while also facilitating the enlistment and stimulation of regulatory T cells (Tregs). M2-like macrophages release many growth factors that are essential for the restoration and renewal of tissues, which encompass VEGF, fibroblast growth factor (FGF), insulin-like development factor 1 (IGF-1), and epidermal growth factor (EGF). These factors stimulate the multiplication and specialization of neural progenitor cells and facilitate the restoration of brain tissues. M2-like macrophages have a crucial function in removing cellular debris and apoptotic cells from the site of damage. The process of phagocytosis aids in the creation of a hygienic environment that is favorable for the healing and regrowth of tissues. Clearing away waste also

helps to avoid more inflammation and injury to the tissue, which is especially advantageous in the case of CP. M2-like macrophages participate in the modification of the extracellular matrix (ECM) by the secretion of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs). This remodeling is crucial for repairing the structural integrity of the brain tissue and promoting the movement and incorporation of neural cells into the affected regions. M2-like macrophages also exert neuroprotective effects through the secretion of neurotrophic factors, including BDNF and GDNF that facilitate the survival and functioning of neurons, safeguard against apoptosis, and enhance the development and restoration of neural connections [96–99].

Only one study included in this review utilized M2-like macrophages derived from peripheral blood (Table 12). In this study [77], 21 patients with CP received an intrathecal injection of an average of $0.8 \pm 0.12 \times 10^6$/kg of autologous M2-like macrophages and were monitored for five years. No significant AEs were recorded. However, 14 patients (67%) had fever, and there were two cases of vomiting as minor AEs. Three months after the cell therapy, 15 CP patients (71.4%) showed a notable reduction in spasticity, enhanced muscle strength, and improvements in gross motor and cognitive functions as assessed by GMFM, PDMS, and Ashworth scale evaluations. It was reported that these improvements were sustained during the 5-year follow-up period. Importantly, when cytokines and growth factors levels in responding and nonresponding patients were compared, it was found that CP patients who positively responded to cell therapy had significantly higher levels of brain-derived neurotrophic factor (BDNF) and showed a strong tendency towards increased VEGF. This suggests that the presence of higher levels of BDNF and VEGF may be indicative of a more favorable response to cell therapy in CP patients. Further research is needed to fully understand the role of these factors in predicting treatment outcomes.

Overall safety of cell therapies for cerebral palsy

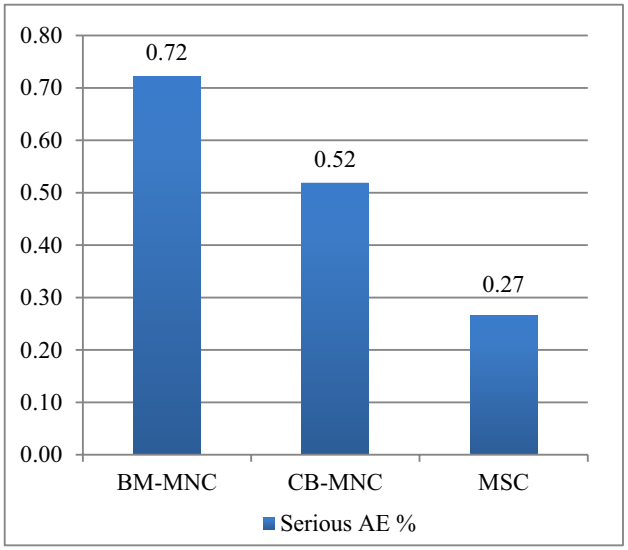
A total of 1474 CP patients have received cell therapy among the studies included in this systematic review. Among all patients, a total of six serious AEs were reported (0.41%). Two of them were seizure incidences that occurred in one of the BM-MNC studies; three of them were hypertension, acute wheeze, and hypokalemia incidences that occurred in one of the CB-MNC studies; and the last one was a worsening in epilepsy that occurred in one of the MSC studies. There were neither mortalities nor tumor formations related to the cell therapy reported in any of the studies. Overall, the incidence of serious AEs related to cell therapy in CP patients was very low across

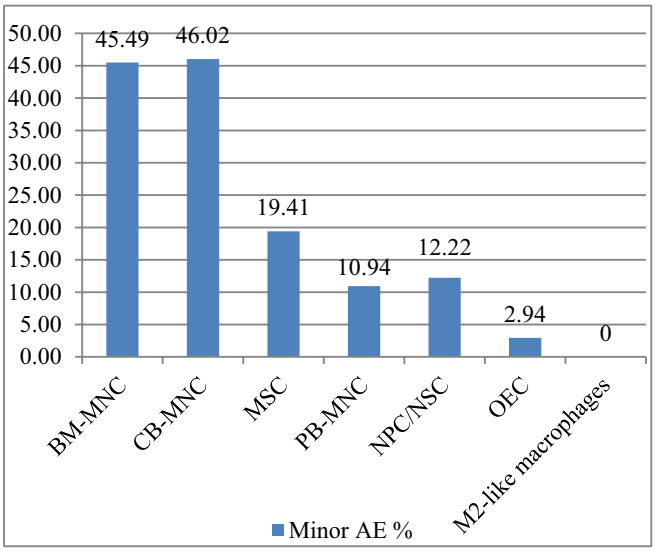
Table 12 Studies conducted with M2-like macrophage cells

Study reference	Number of patients enrolled Tre. Con.	Cell dosage and administration route	Summary of outcome	Adverse events	Follow-up time (months)
Chernykh et al. (2014) [77]	21 –	A single intrathecal administration of an average of $0.8 \pm 0.12 \times 10^6$/kg (range, $0.18–2.15 \times 10^6$/kg) autologous M2-like macrophages	Significant decrease in spasticity Significant improvement in cognitive functions, muscle strength, gross and fine motor activities	No AEs occurred	60

AE adverse events

Table 13 Percentage of adverse events occurred among all studies included in this review





the studies. The absence of mortalities or tumor formations is a positive outcome for the safety profile of cell therapy treatment approach.

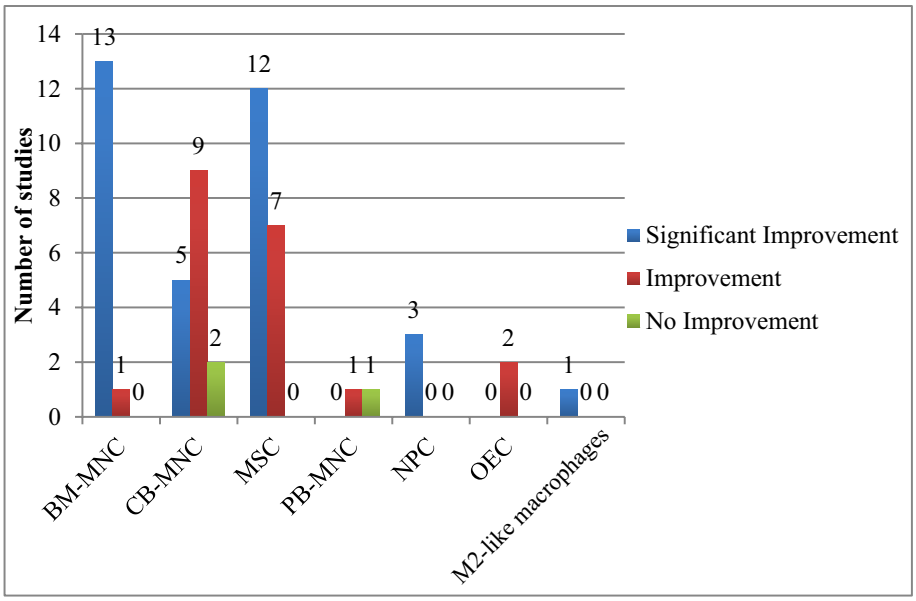
Patients experienced a total of 485 minor AE incidences (32.9%). The majority of minor AEs were reported to be mild, self-limiting, with no long-term consequences and eliminated with appropriate treatments. It should be also noted that some of these minor AEs may not be actually related to the cell therapy. For example, upper respiratory tract infections occurred in CB-MNC and MSC studies, irritability, influenza and other reported infection incidences reported in CB-MNC studies may be caused by other environmental factors rather than the cell therapy. Comparing AEs occurred among all cell therapy studies included in this review, it can be seen in Table 13 that highest number of minor AE percentage was seen in CB-MNC and BM-MNC studies (46.02% and 45.49%, respectively). Some of the most common AEs encountered were related to infusion reactions such as fever, headache, nausea, and vomiting. Because these symptoms were especially encountered in studies utilized with intrathecal administrations, it may be suggested that these AEs may be linked to an increase in intracranial pressure during cell administration. Following CB-MNC and BM-MNC studies, percentage of minor AEs reduce dramatically in MSC studies (19.41%). Subsequent MSC trials, studies conducted with NPC/NSC, PB-MNC, OEC and M2-like macrophages had lower minor AE incidences (12.22%, 10.94%, 2.94% and 0%, respectively). But because there were only three NPC/NSC, two OEC, and one M2-like macrophage studies up to today to our knowledge, more clinical studies are required to assess the safety of these cell therapy products due to the limited number of studies completed in comparison to MSC, CB, and BM-MNC studies. The safety profiles of various cell treatment regimens in this review were generally positive, with a low occurrence of AEs, especially in MSC studies.

Efficacy of different cell therapy strategies for cerebral palsy

Out of 60 cell therapy studies included in this review, only three of them concluded their studies reporting no beneficial effects for CP patients. One of them was a CB-MNC study [41, 42] and the other one was a PB-MNC study [52]. Although no significant difference in motor functions between placebo and treated groups was reported in the CB-MNC study, it did reveal that patients who were administered cell doses above 20×10^6/kg exhibited marked enhancements in brain connectivity and motor function compared to those who received less than 20×10^6/kg, underscoring the critical role of cell dosage in achieving optimal therapeutic outcomes [41, 42]. Three studies included in this review were not designed to evaluate the efficacy of cell therapies, but the safety, feasibility and the importance of a high-quality cell product was emphasized [32, 37, 44]. Apart from the aforementioned studies, 54 out of 60 cell therapy studies reviewed reported positive therapeutic benefits of various cell products for treating CP, indicating an encouraging outcome for cell therapies. While 34 studies reported significant clinical improvements in certain aspects of patients, the clinical improvement was not enough to be statistically significant in 20 studies.

Out of 14 BM-MNC studies, 13 of them [18–20, 22–31] concluded their study reporting significant improvements in gross motor and cognitive functions of CP patients, which is very promising. But it should also be noted that, due to ethical reasons, none of the BM-MNC studies utilizing an intrathecal administration of BM-MNCs included a

Table 14 A summary of clinical outcomes of different cell therapy approaches showing the number of studies resulted with significant clinical improvement, improvement and no improvement



control group in their study. The significance of the clinical improvement was evaluated according to the anticipated progress of a CP patient without cell therapy. Five CB-MNC studies [33, 34, 36, 38, 48] concluded their trials with significant clinical improvement, in four of these studies the results were compared to a control group [34, 36, 38, 48]. Nine other CB-MNC studies were concluded reporting clinical improvement but not enough to be statistically significant [35, 39, 40, 43, 45–47, 49, 50]. All MSC studies included in this review were reporting clinical improvement in muscle strength, gross motor and cognitive functions of CP patients. In twelve of them the improvement was significant [53, 54, 56, 58, 59, 61, 65–70] and in five of these studies [54, 61, 65, 68, 70] the clinical improvement was compared to a control group. All three NSC/NPC studies [72–74] have reported significant improvement in gross motor functions compared to a control group, which is very promising and both of the OEC studies[75, 76] reported improvement in gross motor functions. The only study conducted with M2-like macrophages [77] also reported a significant improvement in cognitive functions and muscle strength.

After reviewing all trials, it can be claimed that BM-MNC and MSC studies reported more favorable results in treating CP as 13 out of 14 BM-MNC studies and 12 out of 19 MSC studies reported significant clinical improvement in gross motor and cognitive functions of CP patients. Also, none of the BM-MNC and MSC studies concluded their study without any improvements in the patients. Additional clinical trials are necessary for NPC/NSC, OEC, and M2-like macrophage cell therapy products to enhance our comprehension of the effectiveness of these treatment approaches. Table 14 summarizes the clinical outcomes of studies included in this review.

Discussion

Although congenital abnormalities are seldom pinpointed as primary causes, environmental variables, along with genetic susceptibilities, significantly contribute to the genesis of CP syndromes. The pathogenesis involves these factors affecting a brain that isn't fully developed, leading to damage mostly seen in the white matter of babies born before their due dates and in the gray matter and brainstem nuclei of babies born on time [100]. Studies investigating the effectiveness and safety of cell treatments for CP demonstrate intriguing potential for enhancing the quality of life and clinical outcomes in different aspects of patients with this complex neurological condition. MSCs and BM-MNCs have been highlighted as promising candidates in this review for their superior therapeutic benefits on CP, showing considerable improvements in gross motor skills and cognitive functions with a lower occurrence rate of AEs.

MSCs can develop into connective and muscular tissue cells as well as non-mesodermal cells, specifically brain lineage cells like neurons and glia. Studies have shown that under NSC culture conditions, MSCs may generate neurospheres and organoids [101, 102]. MSCs can be used to treat several neurological illnesses due to their neuroprotective properties, their role in neurogenesis, and their potential to differentiate into neuron-like cells and show specific brain markers [103, 104]. MSCs have demonstrated the ability to protect brain cells from Aβ toxicity, reduce neuroinflammation, decrease cell damage in the hippocampus, and enhance cognitive abilities in animal models. Thus, MSCs are considered a promising therapy for a range of brain disorders and illnesses caused by neuroinflammation [105]. In view of the aforementioned features of MSCs, the pathophysiology

of CP, and the clinical evidence from the studies included in this review, it can be claimed that MSCs exhibit great potential in the treatment of CP and increase the quality of life of patients with the condition.

Despite the lack of control groups, the data suggests that intrathecal BM-MNCs infusions are also beneficial for CP patients. BM-MNCs consist of hematopoietic stem cells (HSCs), MSCs, and endothelial progenitor cells (EPCs), along with lymphocytes, monocytes, and macrophages. The cytokines produced by these cells have immunomodulatory and neurotrophic effects that aid in the regeneration, repair, and replacement of the central nervous system [106–108]. BM-MNCs and CB-MNCs differ in the quantity and diversity of stem cell populations. Most of the stem cells in CB-MNCs are hematopoietic, while the stem cells in BM-MNCs consist of both hematopoietic and MSCs. Another distinction is in the age of the cells. Bone marrow is the origin of BM-MNCs, whereas umbilical cord blood from a newborn is the source of CB-MNCs. CB-MNCs may exhibit increased proliferative capability and reduced immunogenicity in comparison to BM-MNCs [109–112]. BM-MNCs and CB-MNCs are similar; however, studies included in this review on BM-MNCs have demonstrated better efficacy for CP patients than studies with CB-MNCs. The main difference between BM-MNC and CB-MNC studies was the delivery method. While 13 out of 14 BM-MNC studies utilized single or multiple intrathecal administrations, 14 out of 17 CB-MNC studies used single or multiple IV injections. Intrathecal administration has several advantages, has fewer side effects, and is widely considered safe. It is a suitable delivery method for neurological conditions like CP since it is less invasive and provides a direct route to the brain without a blood–brain barrier [112, 113]. This may be the reason why BM-MNC studies included in this review were reported to be therapeutically more beneficial than CB-MNC studies; even though a higher average cell dose was utilized among CB-MNC studies (average cell dosage used was 13.98×10^6/kg for BM-MNCs studies and 23.77×10^6/kg for CB-MNC studies). It should be noted that, if intrathecal administration is preferred by physicians, discarding an equal volume of cerebrospinal fluid before administering the cell therapy product may reduce incidences of these minor AEs. Additionally, monitoring patients closely for signs of increased intracranial pressure during and after administration may help in the early detection and management of these symptoms. Overall, proactive measures can be taken to minimize the occurrence of minor AEs associated with intrathecal administrations. It's also important to know that because CB-MNC products come in large amounts (usually about 25 ml) cryopreserved products contain much higher amounts of cryoprotectants like DMSO. This means that even if the product is washed before use, it may still contain higher amounts of DMSO after it has thawed. This DMSO residue may induce AEs like fever, nausea, and seizures [114], which may explain the higher number of minor AE incidences in the CB-MNC studies included in this review. Unlike BM-MNCs, which can be administered freshly after isolation step without cryopreservation processes, CB-MNCs are collected during delivery, processed, and always cryopreserved directly for future use.

However, the nature of MSC products produced in appropriate cGMP facilities offers a benefit over CB and BM-MNC products by ensuring high purity and predictability. CB and BM-MNC products contain a variety of cell types, such as hematopoietic stem cells (HSCs), MSCs, endothelial progenitor cells, lymphocytes, monocytes, red blood cells, and other hematopoietic lineage cells [115, 116], as these cells are simply isolated from tissues by centrifugation steps. In contrast, MSC products are cultured post-isolation under specific conditions to achieve a high yield, pure MSC product. While the diversity of cell types in CB and BM-MNC products may lead to unexpected and unpredictable consequences, high purity MSC products can be more predictable with fewer unintended effects. Also, MSCs can be used allogenically as they are HLA-DR negative cells and not expected to create an immune response in the receiver, whereas CB and BM-MNC products have a higher expression of HLAs and should either be used autologously or from a HLA-matched donor [117, 118]. This may also be another reason for the lower occurrence of minor adverse events in MSC therapies. This variability underscores the importance of understanding the immunophenotypic characteristics of different cell populations for various therapeutic applications.

Conclusion

Cerebral palsy, a non-progressive neurological disorder, significantly impacts motor function and daily living activities, highlighting the paramount importance of advancing treatments to enhance the quality of life for affected individuals. After reviewing 60 cell therapy studies conducted after 2010, our study emphasizes that intrathecal application of MSC and BM-MNC therapies showed significant therapeutic advantages, with MSC trials having a superior safety profile compared to other cell therapy strategies. While trials on BM-MNC and MSC have yielded inconsistent results, with certain studies indicating superior efficacy for specific outcomes, it is important to consider that the effectiveness of these therapies can be influenced by factors such as cell dosage, transplantation route, and frequency of administration [119, 120]. Therefore, randomized, double-blind clinical trials comparing different cell types are necessary to draw definitive conclusions about their relative efficacy in treating CP. As there are only a limited number of studies

conducted with NPCs, NSCs, OECs, and M2-like macrophages, the promising results these studies have reported should be confirmed with more clinical trials utilizing these cell therapy products. In the future, thorough assessment of safety parameters and careful selection of patients will be crucial to improving results and reducing AEs in efforts to improve the treatment options for individuals with CP. The cell dosages used can significantly impact the results of cell therapies. Tables 3, 5, 8 demonstrate a significant difference in cell doses among investigations of the same cell product types. Further research is needed to determine the ideal cell doses to enhance the therapeutic benefits of cell treatments. In future studies, it is recommended to use "cells per kg body weight" units for a more accurate and standardized manner of measuring cell doses, as the total cell amount applied does not specify the actual dose considering the age and weight of different patients (unless the cell product is a transplantable patch or the intervention is limited to a local area). This will also facilitate accurate data exchange among cell therapy researchers and physicians. Conducting clinical trials utilizing cell treatments for CP requires extensive ethical considerations to guarantee the safety and welfare of participants, particularly due to the delicate condition of the patient population, which frequently includes children. It is crucial to adequately handle ethical considerations in studies, including getting informed consent from patients or their legal guardians, ensuring equitable selection of participants, preserving transparency, adhering to good clinical practices (GCP), and safeguarding confidentiality. Additionally, researchers must also be prepared to address any unexpected adverse events that may occur during the trial, taking appropriate action to protect the well-being of the participants.

Ultimately, the culmination of our findings not only underscores the promising potential of cell therapies in ameliorating the burden of CP but also emphasizes the imperative of continued research efforts to refine treatment protocols, enhance safety profiles, and ultimately improve the lives of those living with this complex neurological condition.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare that they have no competing interests.

Ethics approval Not applicable.

Consent to participate Both authors hereby provide our consent to participate in the submission of the manuscript titled "A Systematic Review of Cell Therapy Modalities and Outcomes in Cerebral Palsy" to the Molecular and Cellular Biochemistry Journal. We understand and agree to the following terms and conditions: We confirm that we have read, reviewed, and contributed to the creation of the manuscript titled "A Systematic Review of Cell Therapy Modalities and Outcomes in Cerebral Palsy". We are aware of its content and have made substantial intellectual contributions to its development. We understand that the submission of this manuscript is being made to the Molecular and Cellular Biochemistry Journal and that it is subject to the journal's peer-review process and editorial policies. We acknowledge that we have reviewed and complied with the journal's author guidelines and ethical standards for manuscript submission, including the guidelines on authorship, originality, and conflicts of interest. We understand that the manuscript may be reviewed by independent experts and that revisions may be required before publication. We agree that the corresponding author, Ayberk Akat Ph.D., is authorized to act on our behalf regarding all matters related to the submission, review, and publication of this manuscript, including correspondence with the journal's editorial team. We affirm that the content of this manuscript is original, has not been previously published elsewhere, and is not under consideration for publication in any other journal. We understand that if the manuscript is accepted for publication, it will be made available to the public through the Molecular and Cellular Biochemistry Journal and other platforms. We grant the Molecular and Cellular Biochemistry Journal the right to use and distribute the manuscript in accordance with its publication policies, including online and in print. We confirm that all co-authors have been informed of and consent to the submission of this manuscript to the Molecular and Cellular Biochemistry Journal. We acknowledge that any changes to authorship, conflicts of interest, or other relevant information will be promptly communicated to the journal's editorial team. We hereby provide our consent to participate in the submission of this manuscript and confirm that we have reviewed and agree to the terms outlined above.

Consent for publication All authors reviewed the results and approved the final version of the manuscript to be published. All authors hereby give consent for the publication of our personal information in Molecular and Cellular Biochemistry Journal. This information includes, but is not limited to, our name, age, sex, and any other information that is included in the article. We also understand that we are granting the publisher the exclusive right to publish the article in all languages, in whole or in part. We retain the right to use the article for our own purposes, such as teaching, lecturing, and presenting at conferences.

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