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Review Article

Therapeutic Potency of Cord Blood Stem Cells in Patients with Cerebral Palsy: A Systemic Literature Review

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ABSTRACT

Background: The main objective of this study was to systematically review the reported potency of cord blood stem cells in treating patients with neurological disorders such as cerebral palsy.

Methods: PubMed, Scopus, and Cochrane were searched thoroughly on September 2016 using the following search terms: "Umbilical cord blood stem cells" AND "development" AND "cerebral palsy" to find articles in which the umbilical cord blood stem cells were used to treat patients with cerebral palsy. Only English-language studies conducted on patients with cerebral palsy were included and used for data extraction.

***Results*:** Of a total of 77 articles found in the database search, only 6 papers fully met the inclusion criteria. The results showed successful treatment with cord blood stem cells in 165 patients with cerebral palsy.

Conclusion: Studies on both human and animal models have shown the beneficial effects of stem cell therapy in the treatment of various neurological diseases. Data presented that cord blood stem cells can be considered as a main therapeutic strategy to treat patients with cerebral palsy. In addition, it is shown that cord blood stem cells significantly improve motor function, cognition, and memory in patients with cerebral palsy.

Keywords: Cerebral palsy, Stem cell therapy, Umbilical cord blood cells

Introduction

Cerebral palsy is described as a range of disorders of motor and postural development. Cerebral palsy usually includes a series of typically non-progressive brain disorders, which is characterized by abnormal postures (1). Cerebral palsy is a major cause of disability in early childhood. It may cause neurological disorders and lifelong brain dysfunction. Depending on the area of the brain damage, cerebral palsy can be categorized into different forms. Four main types of cerebral palsy include spastic, dyskinetic, ataxic, or mixed, which is observed in patients who have more than one movement disorders (2).

The prevalence of cerebral palsy across the world is 3.3 per 1000 population, and approximately 80% of this population has spastic cerebral palsy. Among children with cerebral palsy, 8% have a range of disorders such as autism and 35% are diagnosed with epilepsy (3). Cerebral palsy is typically caused by brain damage or cerebral anomalies. Although many of these problems occur in the embryonic period, but it can occur at any other time, for example during the first two years of life or when the brain is still evolving. In some patients with cerebral palsy, some parts of the brain may be damaged due to the reduced levels of oxygen (hypoxia) leading to impairment in movement, learning, hearing, vision, and cognitive skills (4-6). Almost

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80% of patients with cerebral palsy have some difficulties in speaking. Nearly three-quarters of all the children with cerebral palsy have low visual acuity, and half of them have gastrointestinal and feeding problems (7). Some infants that are born with asphyxia do not normally encounter serious health problems by using appropriate medical care, but some of this population may suffer from brain defects, which may lead to neural disorders in the brain resulting in a child with cerebral palsy or motor neurons disability(7).

Since the regeneration of the brain after birth in normal conditions does not occur or is very slow, using cutting edge and modern technologies may help to minimize morbidity in these children. Also, because the treatments carried out so far have not been able to improve the healing process of this disease, it is suggested that the use of stem cells, especially cord blood stem cells (CBSC) can be a step towards the improvement of the nervous system disorders (8). Recent reports indicate that using stem cells may be an effective approach to treating this type of disease (9). Umbilical cord blood stem cells are usually collected from the umbilical cord soon after birth. Efficacy of these cells as a new therapeutic approach is shown in treating certain diseases including neurological impairment and blood cancers such as leukemia (10, 11). Therefore, in this review we aimed to systematically review the literature in which umbilical cord blood stem cells have been used to treat cerebral palsy.

Methods

Literature search strategy

PubMed, Scopus, and Cochrane were searched systematically to find articles in which the umbilical cord blood stem cells were used to treat patients with cerebral palsy. The retrieved articles were searched for "umbilical cord blood stem cells" and "cerebral palsy" in the title, keywords, and abstract on February 2016, and then the results were limited to finding "developmental scores" in the selected papers. Relevant articles with the following search terms: "Umbilical cord blood stem cells" AND "development" AND " cerebral palsy" were selected and reviewed by two independent reviewers. Irrelevant articles were omitted in several step by step processes of article selection. Full text of the relevant documents was obtained and fully reviewed for data extraction. To include other relevant articles and minimize the possibility of missing other relevant data, the reference lists of the included articles were also searched manually.

Study selection

There was no time limitation for the included articles, but in order to minimize any misinterpretation of data in further processes of data extraction, only English-language articles were included in the study. Articles of all types including cross-sectional studies, clinical trials, case series, and cohort studies were included in this study, while review articles and meta-analyses were excluded. The inclusion criteria for the selection of articles were documents in which the umbilical cord blood stem cells were used to treat patients with cerebral palsy. Irrelevant or duplicate documents were omitted in the first step by reviewing the titles and abstracts of the papers. Articles on stem cells with the origin of other than umbilical cord blood employed to treat cerebral palsy patients, as well as all the in-vitro studies and those conducted on animal models were excluded from further assessment.

Data synthesis

Data including the name of the first author, country of origin, publication date, study design, and concluded results were extracted. All the available data including the number of patients, type of study, demographic data and concluded results were obtained as possible. The extracted data were categorized based on the results reporting the developmental effects of umbilical cord blood stem cell therapy in patients with cerebral palsy. In some of the included studies, the effects of other drugs were also studied as possible confounding factors. To confirm the improved behavior and performance of patients with cerebral palsy, mental development tests were performed. Different test methods including F-fluorodeoxyglucose positron emission tomography (F-FDG-PET/CT), diffusion tensor images (DTI), gross motor function classification system (GMFCS), gross motor function measure (GMFM), fine motor function Measure (FMFM) and manual ability classification system (MACS) were applied to investigate the efficacy of treatment with cord blood stem cells. These methods were also obtained and analyzed as possible variables. All the processes of data extraction and study selection were based on the recommendation of PRISMA 2009 checklist.

Result

Search results

From 77 articles found in the databases

search, 8 papers were found in PubMed, 69 records in Scopus, and no papers were found in Cochrane. Of them, only 14 articles seemed relevant to the objective of this study. After carefully reviewing the articles, 5 papers were excluded because they were conducted in animal models. Moreover, three articles were excluded due to full text unavailability or language irrelevancy, and full text of four articles that met the inclusion criteria was obtained for data extraction. Figure 1 shows the step by step selection process of the articles.

Description of the included studies

A total of 165 patients with cerebral palsy had been studied in the included studies. The populations of the studied articles were children with the mean age of 57.76 months (age range: 6 months to 20 years). These patients received an average of 13.33 months of treatment and follow-up care. However, the duration of treatment varied from 4 weeks to 28 months among the included studies. The number of studied patients varied from 2 cases of poliomyelitis to 96 patients in a randomized double-blind clinical trial. Of these patients, 95 were male.

Study results

Patients with cerebral palsy often suffer from behavioral and functional impairments. In the included studies, patients were treated with embryonic cord blood stem cells. The results revealed that the efficiency of this type of treatment varied among the studies, but in all of

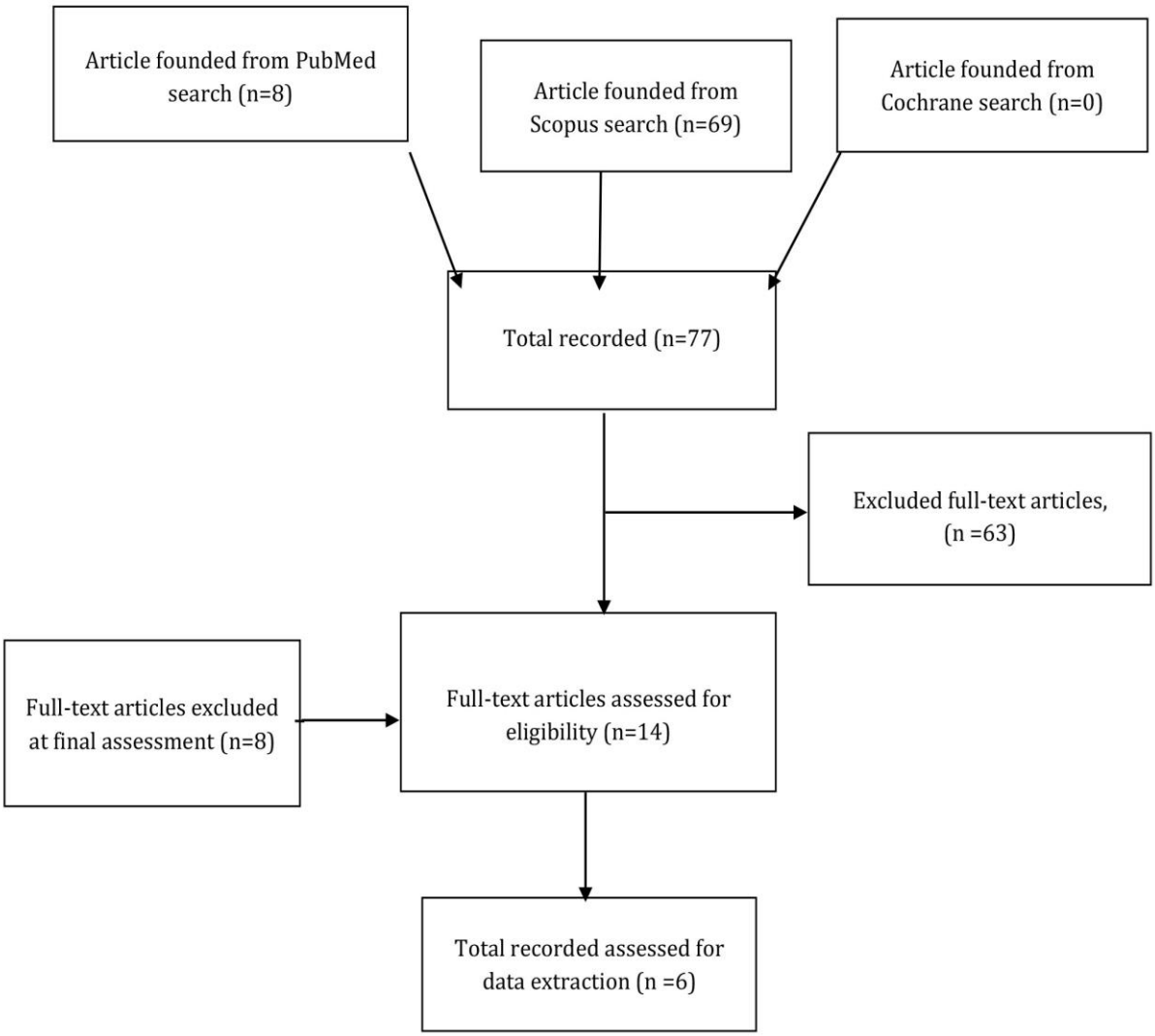

Figure 1. Flowchart for selection of studies

Table 1. Data and variables extracted from the included studies

NO	First author, Country (Year)	Study type (treatment period) ®	Study population*	Number of patients	Methods of detection **	Results
1	Min K, Korea (2013) (12)	DBRCT (6 months)	cerebral palsy	96	F-FDG-PET/CT, DTI	Motor and cognitive improvement
2	Crompton KE, Australia (2014) (13)	CT (-)	cerebral palsy	12	GMFCS	Motor function improved
3	Papadopoulos KI, Thailand (2011) (14)	CR (28 months)	cerebral palsy	2	GMFCS	Functional outcome improved
4	Lee YH, Korea (2014) (15)	SAPS (24 weeks)	cerebral palsy	20	MRI-DTI, GMFCS, GMFM, MACS	Motor function improved
5	Mino Kang,Korea(2015) (16)	CT (6 months)	cerebral palsy	17	F-FDG-PET/CT, Cytokine, MMT, GMFM, edition BSID-II, GMFP, PEDI	Functional outcome improved, innate immune responses potentially mediate the therapeutic efficacy of UCB
6	XIAODONG WANG, Chinese (2015) (17)	SAPS (6 months)	cerebral palsy	16 (8 pairs)	GMFM, FMFM	Motor function improved

® DBRCT: Double-blind, randomized clinical trial, CT: Clinical trial, CR: Case report, SAPS: Single arm pilot study,
* Cerebral palsy
** F-FDG-PET/CT: F-fluorodeoxyglucose positron emission tomography, DTI: Diffusion tensor images, GMFCS: Gross motor function classification system, GMFM: Gross motor function measure, MACS: Manual ability classification system, MMT: Manual muscle testing, BSID-II: Bayiey Scales of infant development, GMFP: Gross motor performance measure, PDEI: Pediatric Evaluation Disability Inventory, FMFM: Fine Motor Function Measure

these studies, brain function improvement and neurodevelopmental evaluation were reported after injections of fetal cord blood stem cells. The results of these studies also presented a significant improvement in cognitive impairment and cerebral dysfunction after treatment with cord blood stem cells. Therefore, according to the data obtained in this study, cord blood stem cells can be considered as an effective therapeutic strategy in the treatment of patients with cerebral palsy.

Discussion

The beneficial effects of stem cell therapy in the treatment of various diseases have been investigated in both human and animal models (18, 19). The fetal umbilical cord blood cells are currently used to treat over 80 diseases, and these cells have a high ratio of hematopoietic cells transplantation (20). Our findings showed that injection of human umbilical cord blood mononuclear cells (HUCBMC) can help to improve mice with cerebral palsy (21). Results also demonstrated that learning, memory, and motor functions significantly improve in mice with neural, movement, and memory impairments after treatment with cord blood mononuclear stem cells. Studies claim that the quality of treatment has increased in infants with cerebral palsy by using the umbilical cord blood stem cells (12).

Mesenchymal stem cells, which are multi-potent regenerable cells and are identified in a variety of tissues such as bone marrow, adipose tissue, and umbilical cord blood, were also successfully used to treat patients with cerebral palsy (22, 23). Moreover, these cells can be successfully used for the treatment of neurological disorders such as cerebral palsy, Parkinson's disease, Huntington's disease, and brain injuries (24-26). Other studies conducted on patients with cerebral palsy showed that mesenchymal stem cells are helpful in the treatment of patients with motor dysfunction, and the results showed that gross motor function measure (GMFM) significantly improved after three months of treatment (27). Treatment with allogeneic UCB alone improved motor function in children with cerebral palsy and proved to be therapeutically effective. Assays of inflammatory markers in the blood showed that innate immune responses potentially mediate the therapeutic efficacy of UCB (28). One study suggest that stem cells can promote the repair of CNS damage and can ameliorate symptoms in children with cerebral palsy; these improvements display individual differences. Identical twins with the same hereditary background had a significant consistency in their responses to the stem cell transplantation, whereas individuals with different hereditary backgrounds showed

significant variations (28). Moreover, many clinical studies are in progress on the influence of fetal umbilical cord stem cells in children with cerebral palsy (https://www.clinicaltrials.gov).

In this study, we systematically reviewed the effect of cord blood stem cells on the development and improvement of the brain in patients with cerebral palsy. The data obtained from the included studies show that CBSCs have desirable therapeutic potency in the treatment of patients with cerebral palsy. Overall, the results of these studies showed that of 165 patients with cerebral palsy, 40% showed brain development with the use of stem cells of fetal cord blood.

Conclusion

According to the results of the included studies and based on the obtained data, it is concluded that cord blood stem cells can be considered as a main therapeutic approach to treat patients with cerebral palsy since cord blood stem cells can significantly improve motor, cognitive and memory function in patients with cerebral palsy.

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Conflicts of interests

None declared.

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