Brain & Development 38 (2016) 699–705

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Review article

Stem cells therapy in cerebral palsy: A systematic review

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Received 9 January 2016; received in revised form 5 March 2016; accepted 8 March 2016

Abstract

The aim of this study was to systematically present the best available stem cell therapies for children with cerebral palsy (CP). The databases Medline, PubMed, EMBASE, and the Cochrane Controlled Trials Register for RCTs were searched for studies published from 1967 to August 2015. Systematic reviews, randomised controlled trials (RCTs), controlled trials, uncontrolled trials, cohort studies, open-label studies, and a meta-analysis were analysed.

Of 360 articles, seven fulfilled the inclusion criteria: one RCT and six were open-label trials. In these studies, one application of stem cells for children with CP was typical, and the total number of cells administered to patients ranged from 10^6 to 10^8/kg. Different routes of cell delivery were used, though in most studies motor development was applied as an indicator of primary outcomes. In three articles, neuroimaging studies were also implemented to confirm the efficacy of the therapies. Observation periods varied from 3 months to 5 years, and patients' tolerance of the therapy was generally good. Stem cell therapy may improve some symptoms in patients with CP, though larger studies are needed to examine the impact of stem cell therapy upon CP.

Keywords: Stem cells; Cerebral palsy; Systematic review

1. Introduction

The most frequent neurological disorder associated with perinatal injury of the developing brain is cerebral palsy (CP) [1]. A lifelong disorder, CP is a syndrome encompassing a range of childhood movement and posture disorders, as well as associated impairments such as intellectual ability and epilepsy. CP's overall prevalence has remained stable during the past 40 years, at 2–3 cases per 1000 live births, despite changes in antenatal and perinatal care [2]. The difficulty of diagnosing the syndrome stems from its various classifications, since CP can be defined according to anatomical brain lesions in the cerebral cortex, pyramidal tract, extrapyramidal system, or cerebellum; by clinical symptoms and signs such as spasticity and dyskinesia; by the topographical involvement of extremities as in diplegia, quadriplegia, and hemiplegia; by the timing of presumed insult prepartum, intrapartum, or during the postneonatal period; and by the classification of muscle tone as isotonic, hypotonic, or hypertonic [3].

Most cases of CP arise from interference during brain development in utero. In that sense, CP is the effect associated with cerebral developments such as schizencephaly during the first trimester, periventricular white

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http://dx.doi.org/10.1016/j.braindev.2016.03.002
0387-7604/

matter damage during the second trimester, and with cortical and deep grey matter damage during the third trimester [4].

Though no fully effective therapy for CP is currently available, an alternative to medically proven methods for patients with CP is stem cell therapy, which during last few years has been the subject of much research focused on CP [5]. The first use of stem cells occurred in 1988 in the context of Fanconi anemia (FA) [6], after which time stem cells, especially that of umbilical cord blood (UCB), experienced increased use as a source of hematopoietic stem cells. UCB stem cells have additionally been administered to children with metabolic disorders involving cerebral dysfunction [7], and research has shown that stem cells were also effective against various neurologic diseases [8]. In terms of therapeutic purposes for CP, stem cells neuroprotective properties from anti-inflammatory and anti-apoptotic activities [5].

Many types of mature and stem cells have been used for experimental and early-phase clinical treatments of CP, whose related studies have typically employed intraparenchymal, intrathecal, and intravenous delivery [9]. However, given the scarcity of information regarding the efficacy of this new treatment, in the present study we report a systematic review of international literature addressing stem cell therapy in children with CP.

2. Methods

2.1. Systematic literature search

Prior to a search of the bibliography, we rephrased our research questions to facilitate the interpretation of literature sought. Based on our rephrasing, we anticipated the different inclusion and exclusion criteria and data to be extracted in every manuscript analysed.

2.2. Inclusion and exclusion criteria

2.2.1. Study population

We required the population of each study to consist exclusively of patients diagnosed with CP.

2.2.2. Study design

The chief studies of interest were meta-analyses, systematic reviews, randomized controlled trials (RCT) and controlled trials, uncontrolled trials and cohort studies, case-control studies, and cross-sectional studies. Case reports and case series with fewer than five patients with CP were excluded.

2.2.3. Intervention

We accepted all types of stem cell therapy.

2.2.4. Outcome measure

To assess the safety of the therapy, we extracted from each study the number of discontinuations, both primary and secondary, due to adverse events in the treatment group compared to those in the placebo or control group, as well as to the number of significant adverse events reported in each group.

2.2.5. Methodological quality

We appraised the quality of all articles that fulfilled the inclusion criteria. To assess the quality of RCTs, we used the Jadad scale, the impact factor of the journal in which the trial was published, and evidence of statistics using intention-to-treat analysis. The Jadad scale [10] contains two questions to determine appropriate randomization and study masking, along with questions to evaluate the reporting of withdrawals and dropouts that require a yes or no response. Five total points are possible on the scale, in which a higher score indicates superior quality. To assess the risk of bias of RCTs, we also used Cochrane Collaboration's tool [11].

2.2.6. Categorizing evidence

We categorized evidence according to the study design using a hierarchy of evidence in descending order according to quality [12] and reviewed the highest level of available evidence for each intervention in detail. Although studies of the highest level were available, we nevertheless reviewed all remaining categories.

2.2.7. Literature search

Two reviewers independently reviewed the search results to identify any articles that fulfilled the inclusion criteria. Specifying a timeframe from 1967 to August 2015, we conducted searches on Medline, PubMed, Embase, and the Cochrane Central Register of Controlled Trials. Only English-language research conducted with human participants was eligible for inclusion. The search strategy included all terms for stem cells therapy ("stem cell" OR "mesenchymal stem cell" OR "umbilical cord blood" OR "multipotent progenitor cell" OR "induced pluripotent stem cell" OR "oligodendrocyte progenitor cell" OR "embryonic stem cell" OR "fetal stem cell" OR "marrow stromal cell") OR "neural progenitor cells" OR "neural stem cell-like cells" OR "autologous macrophages" combined with the term "cerebral palsy."

We implemented a medical subject heading (MeSH) search with all databases and a keyword search if the MeSH search was unavailable. All MeSH search terms were exploded. We examined the reference lists of reviews and systematic reviews and included any additional studies fulfilling the inclusion and exclusion criteria.

The search of PubMed, the Cochrane Database, and Embase yielded 360 articles, most of which derived from PubMed and all of whose titles and abstracts we read.