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Preclinical progenitor cell therapy in traumatic brain injury: a meta-analysis

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ABSTRACT

Background: No treatment is available to reverse injury associated with traumatic brain injury (TBI). Progenitor cell therapies show promise in both preclinical and clinical studies. We conducted a meta-analysis of preclinical studies using progenitor cells to treat TBI.

Methods: EMBASE, MEDLINE, Cochrane Review, Biosis, and Google Scholar were searched for articles using prespecified search strategies. Studies meeting inclusion criteria underwent data extraction. Analysis was performed using Review Manager 5.3 according to a fixed-effects model, and all studies underwent quality scoring.

Results: Of 430 abstracts identified, 38 met inclusion criteria and underwent analysis. Average quality score was 4.32 of 8 possible points. No study achieved a perfect score. Lesion volume (LV) and neurologic severity score (NSS) outcomes favored cell treatment with standard mean difference (SMD) of 0.86 (95% CI: 0.64-1.09) and 1.36 (95% CI: 1.11-1.60), respectively. Rotarod and Morris water maze outcomes also favored treatment with improvements in SMD of 0.34 (95% CI: 0.02-0.65) and 0.46 (95% CI: 0.17-74), respectively. Although LV and NSS were robust to publication bias assessments, rotarod and Morris water maze tests were not. Heterogeneity (I^2) ranged from 74%-85% among the analyses, indicating a high amount of heterogeneity among studies. Precision as a function of quality score showed a statistically significant increase in the size of the confidence interval as quality improved.

Conclusions: Our meta-analysis study reveals an overall positive effect of progenitor cell therapies on LV and NSS with a trend toward improved motor function and spatial learning in different TBI animal models.

Introduction

Traumatic brain injury (TBI) is major public health and socioeconomic problem that affects both civilians and members of the armed forces worldwide.[1,2] Monitoring by the Centers for Disease Control and Prevention shows that with 1.7 million incidents annually, TBI contributes to 30.5% of all injury-related deaths in the United States. TBI survivors experience long-term disabling changes in physical, cognitive, and psychosocial states, and disease management costs more than $77 billion per year. The scope of TBI ranges from limited focal damage due to cerebral contusion, laceration, or hemorrhage to multifocal damage due to acceleration-deceleration injuries, or both.[3] Both local and multifocal

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damage can lead to clinical conditions that require careful assessment and management to prevent long-term disabilities. The pathophysiology of TBI is complex, and the physiologic response of the brain to injury initiates a cascade of cellular pathways, which left unchecked become pathologic.[4] TBI causes stretching of axons, which causes dysregulation of axonal Na^+/K^+ pumps and an increase in intracellular Ca^{2+} concentrations.[5,6] Increased intracellular Ca^{2+} levels lead to excitotoxicity and neuronal cell death.[7] In addition to disturbances of ionic homeostasis, initiation of inflammatory and immune responses also occurs in the central nervous system after TBI.[8,9] These events contribute to blood–brain barrier (BBB) disruption and the development of cerebral edema.[10]

Considering the complexity of the disease pathomechanism, the development of a therapy that can maintain or restore neuronal function would provide the most comprehensive approach to treating TBI. Progenitor cell therapies hold great promise in TBI because of their inherent biological properties of plasticity, self-renewal, and migration. Transplanted progenitor cells could either regenerate dead neurons or repair damaged neuronal cells by producing neurotrophic factors, scavenging toxic molecules, or by exerting immunomodulatory effects. In the past decade, several preclinical studies have shown promising outcomes using progenitor stem cells in TBI animal models.[11,12] In this study, we performed a meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to evaluate the efficacy of different progenitor cell therapies in animal models of TBI.

Methods

A protocol for article search, data extraction, and analysis was developed by the lead author and agreed upon by all authors (see Supplementary materials). To meet inclusion criteria, studies needed to have an animal model of TBI, administer a progenitor cell therapy that had not been genetically manipulated, and analyze at least one of our four prespecified outcome measures, which were: (1) lesion volume (LV), (2) rotarod test (RR), (3) neurologic severity score (NSS) test, and (4) Morris Water Maze (MWM) test. These outcomes were selected for their wide use, allowing us to compare as many studies as possible. Those studies that were not available translated into the English language, or used concomitant therapies (such as but not limited to gene modification, protein administration, or scaffolding) were excluded as having a confounding therapy.

LV was defined as the volume of the brain injury caused by the TBI injury model (e.g., the volume of injury cavity caused by a controlled cortical injury). The RR test is a locomotor function test where a mouse or rat must balance on a rotating rod, which is gradually accelerated. Longer times on the rotarod denote improved locomotor performance. The NSS was defined as a composite score including motor function, alertness, and seeking behavior. By design, the NSS is scored so that a higher score denotes more severe injury. Therefore, an improvement will be a decrease in the score. The MWM is a behavioral test for spatial learning and memory. For the purpose of our study, we extracted latency to the platform, which is the time it takes for a pretrained subject to find a hidden platform in the water maze.

EMBASE and MEDLINE, accessed through Ovid and PubMed, respectively, were selected for the main article search. Biosis, a database of meeting proceedings and abstracts, was also searched, as well as Google Scholar and the Cochrane Review. These were each searched with a prespecified search entry; our search was designed to be exceedingly sensitive, so that we might capture all possible studies, then exclude those that were not pertinent. Throughout the project the searches were updated with the final search date being November 28, 2016.

Search was performed by two independent investigators, and data were extracted by the two investigators (M.L.J. and A.K.S.). Disagreements were put to a third investigator (C.S.C.) for mediation. Those studies that did not present numerical data and only presented graphical data of their findings underwent graphical data extraction using Adobe Illustrator CS6 software. Those studies that presented only a *P* value and effect direction were excluded. All included studies underwent quality assessment as follows: one point each was assigned for evidence in the manuscript of (1) sample-size calculation, (2) randomization, (3) body temperature control during surgery, (4) avoidance of ketamine anesthesia, (5) approval from the Institutional Animal Care and Use Committee or its equivalent and IRB approval for human subject cell extraction, if applicable, and (6) a statement of disclosures/conflict of interest. Two points were assigned for evidence of blinded outcome assessment. These criteria are a combination of recommendations for quality assessment in the stroke preclinical literature[13] and A Call for Transparent Reporting to Optimize the Predictive Value of Preclinical Research by Landis *et al*.[14]

Data extracted for each outcome included the mean, number of subjects, and standard deviation (SD) for each study arm, as is necessary for meta-analysis of continuous variables. When standard error of the mean was presented, it was converted to SD. Once extracted, the data were entered into RevMan 5.3 (The Cochrane Collaboration, Oxford, UK) for analysis using a fixed-effects model and calculating SMD between control and treatment groups. RevMan 5 uses Hedges' adjusted *g*, which is very similar to Cohen's *d* but includes an adjustment for small sample bias, as is appropriate with the animal studies included in our analysis. Equations used by the software can be found in the statistical algorithms supplement to RevMan 5.[15] Quality score metrics were entered into Microsoft Excel 2010, and simple linear and multiple regression were run in Stata 13 (StataCorp, College Station, TX). Regression analyses were designed to test the two primary hypotheses that (1) increased quality score correlated with a larger treatment effect and (2) increased quality score correlated with a smaller confidence interval. As a secondary outcome, multiple regression model tested the hypotheses that year, cell line, timing of treatment, dose, and type of injury affect the treatment effect size.