Stem Cell Therapy for Neonatal Brain Injury

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KEYWORDS

• Stem cell therapy • Neuroprotection • Mesenchymal stem cells
• Amniotic stem cells • Placental stem cells • Neural stem cells
• Embryonic stem cells • Cord blood

KEY POINTS

- Preclinical studies support efficacy of stem cells in models of perinatal brain injury.
- Mechanisms underpinning these neurotherapeutic effects are not fully understood.
- Systemic comparative analysis of effects of known cells across models is required.
- Randomized clinical trials are ongoing.

INTRODUCTION

To understand how to harness the potential of stem cells as therapeutic agents requires the considered formulation and interpretation of data from studies in animal models of injury and disease. Animal models, despite their limitations, represent

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well-defined biologic systems with levels of complexity and responsiveness comparable in many ways to those of human infants. To model neonatal brain injury, researchers have developed two complementary approaches: (1) a reductionist approach, involving inducing specific cellular and/or molecular mechanisms known to be involved in injury; or (2) recapitulating the supposed causal event.

Although the causes and outcomes of brain injury in preterm and term neonates are far from identical, they share some common cellular and molecular mechanisms. These include the processes of excitotoxicity and neuroinflammation, incorporating microglial activation, proinflammatory cytokine and chemokine production, and toll-like receptor (TLR) activation through the production of injured neural tissues of damage-associated molecular patterns (DAMPs, or alarmins). The importance of these pathways is the generally accepted rationale for using excitotoxic agents (eg, agonists of N-methyl-d-aspartate [NMDA] or a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]-kainate glutamate receptors), proinflammatory cytokines, or TLR agonists to mimic mechanistic aspects of these human brain disorders in animal models.[1–4]

In neonatal brain injury, although there is no definitive consensus about the cause of brain damage, the two predominating hypotheses are a hypoxic-ischemic (HI) origin and a systemic inflammatory origin, linked to pathologies such as chorioamnionitis.[4] Accordingly, to model neonatal brain injury in a causal manner, various animal models have been developed based on (1) acute HI insults (eg, transient umbilical cord [UC] occlusion during late gestation[5]), (2) in utero asphyxiation during delivery,[6] (3) carotid artery ligation combined with transient hypoxia in the early neonatal period,[7] (4) chronic hypoxic insults (eg, protracted hypoxia during either the fetal or early postnatal period[8,9]), or (5) systemic acute or subacute inflammatory insults (ie, administration of the TLR agonists[10] or the cytokine IL-1-beta during either the late fetal or early postnatal periods[11]). See later discussion.[3,12] In addition, investigating groups have developed combined models in which systemic inflammation sensitizes the developing brain to a second HI or excitotoxic insult.[13,14]

Stem cell therapies have been envisaged as having enormous potential to repair and regenerate across many fields of medicine. Although much quality research trialing stem cells in neonatal brain damage has been performed in various laboratories across the world, the data are still confusing and sometimes conflicting. This is likely because each research group uses different animal models, different types of stem cells, and different experimental endpoints or assessments.

This article briefly describes the major types of stem cells, reviews the animal data relating to the use of stem cells to protect and repair the neonatal brain, and mentions any safety concerns, before describing the on-going pilot clinical trials with stem cell therapy in human neonates. The article concludes with what the authors believe are the necessary questions that need answering to move this research forward and determine an optimized design for clinical trials in human neonates with brain injury.

MAJOR TYPES OF STEM CELLS

Characteristics that give stem cells therapeutic value include the capacity for some (but not all) lineages to differentiate under permissive conditions and their antiinflammatory and immune-modulatory functions. Stem cells can be obtained from many different tissues and at all stages of life (**Table 1**).

Embryonic Stem Cells

Embryonic stem cells (ESCs) are derived from the inner mass of blastocysts and can self-renew indefinitely because they are able to maintain an identical phenotype