Mini Review

Sven Wellmann*

Stem-cell therapy in neonates – an option?

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Abstract: Within the fast-growing field of regenerative medicine stem-cell therapy is well established in various hematologic and immunologic diseases and has received a recent substantial boost from the introduction of gene editing and gene transfer technologies. In neonates, for example, regenerative medicine may benefit those with congenital or acquired disease due to prematurity or perinatal hypoxia-ischemia. We compare and contrast the two main approaches – autologous vs. allogeneic – and summarize the recent advances and applications of interventional stem-cell research in perinatally acquired disorders such as intraventricular hemorrhage, hypoxia-ischemia and stroke. After discussing stem-cell sources and routes of administration, we conclude by highlighting the key opportunities and obstacles in this exciting field.

Keywords: allogeneic; autologous; mesenchymal; neonate; stem cell.

Introduction

Ten years ago, before any clinical trials had been done with stem cells in neonates, Gortner et al. reviewed the clinical potential of regenerative medicine in neonatology [1]. There was already a wealth of preclinical studies on the table exploiting stem cells in different neonatal diseases and providing a robust rationale for initiating clinical feasibility and safety trials. The fascinating field of regenerative medicine has since grown to the extent that we can now take stock not only of many more preclinical studies but also of the first completed trials of stem cells in newborn medicine.

In contrast to current clinical strategy which is often confined to symptomatic therapy, regenerative medicine seeks to replace specific cells, tissues or organs damaged by congenital defects or acquired diseases or trauma during whole life. The replacement techniques it uses include cell therapies, tissue engineering, medical devices and artificial organs. In neonatology, the cell and organ defects of interest for stem cell therapy fall into two broad categories: on the one hand, those that are primary and mostly congenital, and on the other those secondary to acquired disease, whether prematurity, acute or chronic oxygen or nutrient deficiency, severe infection or multiple other determinants. Whereas the care concept for congenital defects is mainly repair, that for acquired disease is more complex and is supportive rather than curative.

Two excellent reviews have covered the latest advances in the congenital/prenatal and acquired/postnatal approaches used in pediatric regenerative medicine. The prenatal review covers *in-utero* stem-cell therapy, gene therapy and gene-modified cell therapies in congenital and incurable pediatric disease, before discussing the potential of fetal cells in postnatal treatment and artificial placenta for ex-utero fetal therapies [2]. The postnatal review surveys the gene-, cell- and tissue-based technologies for reconstituting the structure and function of tissues and organs, including the application of biocompatible scaffolds seeded with patient-derived cells [3].

The present review of neonatal stem-cell therapy draws on the latest results achieved in perinatal disorders such as intraventricular hemorrhage (IVH), hypoxia-ischemia and stroke.

Autologous stem cell approaches

Stem cells are characterized by their remarkable ability to divide and renew themselves in an undifferentiated state and to differentiate into many types of cells with specific functions in response to appropriate triggers. They exist naturally as embryonic stem cells or adult stem cells, the latter residing lifelong in almost all tissues as neural, mesenchymal, hematopoietic and other varieties of stem cell. Pluripotent stem cells can be produced artificially from almost all specialized cells by cell engineering, using gene editing and gene transfer technologies.

Therapy that uses the patient's own cells is termed autologous since donor and recipient are identical. The advantages of patient-specific cells include no rejection by

***Corresponding author: Prof. Sven Wellmann**, MD, Klinik St. Hedwig, KUNO Kinderklinik, Steinmetzstraße 1-3, D-93049, Regensburg, Germany, E-mail: sven.wellmann@ukr.de. https://orcid.org/0000-0001-9230-6266

the immune system and no risk of graft-versus-host disease. Many umbilical cord blood (UCB) banks have been established on the basis of these and other safety features, fueled by the contributions of parents viewing stem-cell storage as insurance against potential health emergencies [4].

The potential of autologous UCB-derived stem-cell therapy led a number of perinatal centers worldwide to establish protocols and conduct pilot trials for neonatal disorders such as hypoxic-ischemic encephalopathy (HIE) [5, 6] and congenital hydrocephalus [7]. Despite their safety and considerable clinical promise, these studies encountered major hurdles, such as problems in preparing cells on time and in sufficient amounts to permit scalability of the approach using the patient´s own umbilical stem cells right after birth. A large HIE trial was stopped in the US because of poor recruitment (ClinicalTrials.gov identifier NCT02612155) and not surprisingly, the latest Cochrane review of stem-cell interventions in neonatal HIE failed to identify a single eligible randomized controlled trial (RCT) [8]. Technological advance in boosting cell expansion may be needed before the autologous approach to neonatal disease returns to favor.

Allogeneic stem cell approaches

In allogeneic therapy recipient and donor are different. The main advantage is the cell yield while the main challenge is the immune response. There are at least three ways of countering the shortcomings of the allogeneic approach. First, gene transfer or gene editing techniques can be used to modify stem cells and induce already differentiated cells to become multipotent again. Second, embryonic stem cells offer great potential, while also raising as yet unresolved ethical issues. Third, in many different neonatal and adult tissues mesenchymal stem (or stromal) cells (MSCs) [9] form an important cell population with immunosuppressant and tissue repair properties [10].

The main neonatal sources of MSCs are UCB and Wharton's jelly (umbilical cord tissue [UCT]), both of which are readily accessible and available. In adults larger amounts of MSCs are found in bone marrow and adipose tissue. MSCs are actually present in every tissue as part of the microvasculature. Stem cells harvested from young donors are not only more potent, they also exhibit greater complexity before extensive passaging [11, 12]. The relative availability of MSCs, their favorable storage conditions and the safety data now available from completed and ongoing clinical trials combine to boost the case for MSCs as an effective therapy in a variety of diseases, even as an off-the-shelf medical product.

MSCs have now featured for over 20 years in clinical and laboratory studies relating mainly to adult rather than pediatric medicine. Way over 1,000 clinical trials have been logged in international registries and way over 10,000 patients, mainly adults, have been treated. In addition, over 1,000 mainly private hospitals worldwide offer some form of MSC therapy, often not worth the fees that patients pay. However, largely because of the complexity and variety of the products involved, the FDA has so far approved MSC therapy in only very rare instances.

Current status of mesenchymal stem-cell research in neonates

The author performed a systematic search in August 2022 for interventional stem-cell clinical trials registered in the world's most comprehensive online database, ClinicalTrials.gov, maintained by the US National Library of Medicine. 5772 hits were retrieved for the search term 'stem cell' or synonyms such as 'progenitor cell' or 'blast cell' and 486 hits for 'stromal cell'. Most studies concerned bone marrow transplantation, new conditioning regimens and associated treatments rather than the effect of stem or stromal cells in adults. Filtering for children and using 'neonate' or synonyms such as 'newborn', 'newborn baby' or 'newborn infant' retrieved 78 hits for 'stem cells' and 19 for 'stromal cells'.

Most of the 78 hits involved hematologic or immunologic conditions such as severe combined immunodeficiency, followed by broncho-pulmonary dysplasia (BPD). Only six involved perinatal disease such as IVH, hypoxia-ischemia and stroke. Most of the 19 hits for 'stromal cells' and 'neonates' concerned adults in acute respiratory distress with or without COVID-19 (n=16) given stromal cells from newborn donors. Just three were neonates with IVH, stroke or BPD.

Current status of mesenchymal stem-cell research in neonatal neurologic disorders

Further searches using 'mesenchymal' instead of 'stem cells' or 'stromal cells' retrieved no other studies involving perinatal IVH, hypoxia-ischemia or stroke. Of the eight studies of this perinatal triad registered at ClinicalTrials.gov, only the following four show as completed or as

having published results. They all give ground for hope but, as we shall see, at least one raises insuperable barriers in terms of applicability and scalability:

(1) NCT00818220 was a delayed cord clamping RCT which found an unaltered incidence of IVH but improved motor function at age 2 years in the delayed cord clamping group and discussed the possible effect of stem cells, which is why this study showed up in the search [13]. A recent systematic review and network meta-analysis found delayed cord clamping to be associated with lower mortality and morbidity in preterm infants, including those with IVH, making this is a readily applicable low-cost technique for maximizing neonatal stem cell load [14].

(2) NCT02274428 was a phase 1 trial in 9 patients with severe IVH conducted by Park WS et al. at Samsung University in South Korea. They used intraventricular transplantation of UCB-derived MSCs in the second week of life [15]. The approach proved safe and feasible. Follow-up of the 9 patients is ongoing (NCT02673788) and the formulation of the UCB-MSC-derived product (PNEUMOSTEM) is being investigated in other diseases. UCB-MSC-derived products are sourced from pooled healthy neonate donors, posing considerable quality and regulatory issues, and are thus expensive. Once approved, however, there are virtually no limits on scalability, making this an attractive business model. The intraventricular route provides direct access to the injured region after IVH but is more invasive than the intravenous or intranasal routes. More clinical research is needed to settle debate on the most advisable route of administration.

(3) NCT03635450 is a phase 1 trial in 6 patients by Kurtzberg J et al. at Duke University in North Carolina, administering a UCT-derived allogeneic MSC product for HIE intravenously in the first 48 h of life. The study was due for completion in 2020 but results have yet to be published. UCT-derived MSCs have the same scalability potential as their UCB-derived counterparts, fueling the hope for future off-the shelf medication. Generating MSCs from Wharton´s jelly is a relatively low-cost technique with no burden on the donor [16]. Whether and how tissue origin affects the therapeutic potential of MSCs in clinical settings remains to be explored.

(4) NCT03356821 refers to a phase 1 trial in 10 patients with perinatal arterial ischemic stroke conducted by Benders M et al. at Utrecht University, Netherlands, using bone marrow (BM)-derived MSCs from a single donor given by once-only intranasal administration in the first week of life [17]. Intranasal delivery is intriguing in that it is both noninvasive and – at least in animal studies – effective and had already been proposed a decade ago [18]. Using BM-derived MSCs from the same single donor maximizes in-study comparability at the expense of scalability. Interestingly, an observational study has used the nasal route to administer fresh human milk to preterm infants with IVH [19] and at least one phase 1 trial is currently determining whether fresh human milk can be safely delivered as an intranasal stem cell therapy in preterm infants with IVH (NCT04225286).

Conclusions and outlook

Stem-cell therapy in neonates has reached the clinical research phase. The first phase 1 trials to post results showed that various routes of administration were safe and feasible using a variety of stem-cell products. However, efficacy awaits investigation in RCTs. While a couple more years may be needed for the latest gene editing and cell expansion techniques to drive significant advance in autologous stem cell therapies, allogeneic approaches using pooled UCB- or UCT-derived MSCs have the potential for use as commercial products somewhat sooner. Hence the question: is stem-cell therapy in neonates an option? Yes, it most certainly is, right now. Two simple and low-cost stem-cell interventions await daily worldwide implementation. One is already evidence-based: delayed cord clamping in every delivery, and in preterm deliveries in particular, to maximize the stem cell harvest. The other is exploratory but promising: intranasal administration of the stem cells in fresh mother's milk for infants with a severe neurologic disorder.

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