Narrative Review:
Stem Cell Therapy in Children With Sensorineural Hearing Loss: A Narrative Review

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ABSTRACT

Context: One of the research areas is using stem cell transplantation for treating children's sensorineural hearing loss. Preclinical studies and testing of the stem cell types have been performed in this field, and relative improvement has been achieved.

Objectives: This narrative review has been prepared to study the advancements in hearing regeneration with stem cell transplantation.

Data Sources: The English articles with full-text were searched in PubMed, Scopus, and Google scholar from 2000 to 2020 using keywords of sensory neural hearing loss and stem cell.

Results: In 2018, the first human study was performed with stem cells from the human umbilical cord, which has promising results regarding the safety of the method and its positive effects on hearing.

Conclusions: Autologous stem cell transplantation had induced relative improvement without serious adverse events in children with acquired sensorineural hearing loss. To obtain more evidence, further studies are required with larger sample sizes and in different patients groups.

1. Context

The prevalence of hearing loss is about 5% (466 million people) in the world, and almost 34 million of them are children. The World Health Organization (WHO) estimates that about 900 million people will suffer from hearing loss by 2050 [1, 2]. Sensorineural Hearing Loss (SNHL) is a type of hearing loss caused by damage to sensory hair cells of the afferent nerve pathway. The severity of SNHL can range from mild to profound. The moderate to profound cases certainly require therapeutic management; otherwise, it can result in defects in speech and communication skills. Cochlear Implantation (CI) is the only helpful treatment for profound hearing loss. It is a metal implant placed inside the cochlea. CI is not satisfactory in children with auditory neuropathy. Also, it is costly for patients and the health system.

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Considering the effect of stem cell transplantation in some neurological diseases, stem cell therapy could be a novel therapeutic approach in children with moderate to profound SNHL [3]. The mammalian body tissues, including humans, have Stem Cells (SCs) that remain after birth and can be useful in regeneration medicine for some diseases. There is no evidence of the existence of SCs in nervous and sensory cells of the cochlea after birth [4-6].

Some studies suggest that the existing hematopoietic stem cells from bone marrow in the mature inner ear can differentiate into fibrocytes or resident macrophages, but there is no data about developing them to hair cells [7-9]. However, it is unknown how to activate them, too. Therefore, an alternative strategy of using an external source of stem cells is necessary. Some supporting cells in the cochlea can transdifferentiate to hair cells if they follow the metaplasia pathway [10-12].

Some studies have investigated the role of human stem cells in the replacement of damaged cells in the Corti Organ in animal models. These studies were demonstrated the potential ability of human stem cells in regeneration medicine in the hearing system [13-15].

The survival and differentiation of the stem cells have shown variable and challenging outcomes. The studies have elucidated that some molecular agents and fibroblast growth factors can be effective in inner ear development. The otic progenitor cells are produced from human Stem Cells (hSCs). Under special in vitro conditions, these cells are differentiated to hair cell-like cells and auditory neuron-like cells [16, 17].

Experimental studies have reported the recovery of Auditory Brainstem Response (ABR) following stem cell transplantation in some auditory injuries. There was a limitation in survival, differentiation, and integration of those stem cells in the cochlea, but the observed hearing recovery was theoretically explainable with paracrine signaling by stem cells in the cochlea space [18, 19]. Recently, extensive research has been reported on the role of stem cell therapy for some neurological disorders in children. The reports demonstrated the safety and relative improvement in some disorders such as cerebral palsy, autism disorder, and muscular dystrophy [20].

This review aims to introduce the types of stem cells and routes of transplantation used for hearing regeneration, as well as recent advances for the therapy of SNHL in children.

2. Evidence Acquisition

In this narrative review article, we investigated the literature regarding hearing regeneration with stem cell transplantation. For this purpose, we searched PubMed, Scopus, and Google scholar from 2000 through 2020. The following keywords were used to search in the above databases in the English Language: ([Sensory Neural Hearing Loss] OR [SNHL] AND [stem cell]). After the abstract screening, the full text of related studies was reviewed, and studies about stem cell transplantation in the vestibular system and meeting abstracts, editorials, letters, and commentaries were excluded. An additional manual search was performed using reference lists from the research studies and review articles to identify other eligible studies. Full-text articles for hearing regeneration using stem cell transplantation in animals or humans, especially children, were investigated in this narrative review. We had independently evaluated the studies in terms of the published year, type of sample, and results and discrepancies had agreed using discuss together or a third party as a referee.

3. Results

The types of stem cell in hearing regeneration

Many in vivo and in vitro studies have been conducted to repair damaged cochlea and SNHL. The various stem cell types were applied for transplantation in the cochlea. The majority of transplanted stem cells were xenogenic transplantation [21-23].

There are three types of stem cells in cell regeneration that consist of Embryonic Stem Cells (ESCs), adult stem cells, and Induced Pluripotent Stem Cells (IPSCs) [24]. These cells can present cellular markers of otic progenitor cells in vitro using special protocols and activation of some known signals. The otic progenitor cells, in comparison with primary SCs, had a lower risk of tumorigenesis [16, 25, 26]. These cells could be represented some hair cell markers such as ATOH1, Myo7A, BRN3 in the animal model after 4 weeks of transplantation, but they lacked enough integrated cells and synapses competent in the microstructure of the Corti Organ [16, 27-29]. These differentiated cells to hair cells had not electrophysiologically maturated and developed; perhaps acoustic stimuli can be effective in the maturation process [25].

ESCs are prepared from mammalian embryonic blastocysts with unlimited reproducibility and could differentiate into any three embryonic layers (ectoderm, endoderm, or mesoderm). There are shortcomings for

using the ESCs, including ethical issues due to the destruction of a viable embryo, high probability of transplantation rejection, and tumorigenesis risk after years of transplantation [24, 30, 31].

Adult stem cells are a common sample for stem cell transplantation prepared from the matured tissue of a mammalian. These cells can regenerate and differentiate into specialized cell types from the same tissue or other organs. Their advantages are preparing easily, having fewer moral problems, and posing a low risk of rejection compared to ESCs [32]. The most common adult stem cells used for hearing regeneration are Mesenchymal Stem Cells (MSCs). These cells decrease the risk of transplantation rejection by regulating immune system function and lymphocyte proliferation [33]. MSCs show homing properties and can travel toward injured tissues (inflammation or tumor sites) in mechanisms similar to white blood cell migration and penetration from the endothelial layer. This mechanism defines with the activation of surface adhesion molecules of MSCs and releasing of various cytokines and growth factors such as stromal cell-derived factor, fibroblast growth factor, and platelet-derived growth from damaged tissue [10, 33-35]. MSCs, in comparison with other stem cells, have less expensive and easier preparation and tumorigenesis risk. It has been reported that those cells can convert to neural cells due to neuroprotective property [36, 37]. These cells can be subpopulations from various sources such as bone marrow, peripheral blood, umbilical cord, fat tissue, and other tissues, that the bone marrow is the most critical source [33, 38].

Some preclinical studies reported the expression of specific cellular markers related to hair cells and otic progenitor cells in the differentiated process of MSCs [14, 16, 39, 40]. MSCs are successfully differentiated into fibrocyte-like cells in animal models, and they can play the role of molecular and structural supports for the damaged Corti Organ and auditory epithelium layer [41]. Human MSCs have been demonstrated the capability of transplantation and differentiation in animal models with the different damages of the hearing system, such as injury cells in the Corti Organ, spiral ganglion neurons, or fibrocytes [14, 16, 21, 42-44].

An interesting point about other properties of those cells is the presence of sensitive receptors to mechanical stimulation in the surface of MSC. In some studies, it has been observed that the stimulation of these receptors with sound stimuli has increased proliferation and differentiation of MSCs [16, 45-47].

There is another type of adult stem cell as neural stem cells. Neural stem cells can be derived from some glial cells. The olfactory epithelium, due to its markers, is similar to auditory epithelial markers, so it is an appropriate source for the preparation of those cells. The neural stem cells have specific receptors that bind with potential chemical factors secreted from the Schwann cells of the damaged auditory nerve [48, 49].

The third group of stem cells is the Induced Pluripotent Stem Cells (IPSCs) derived from each somatic tissue in vitro and then are reprogrammed to differentiate into cells from any of the three germ layers [50, 51]. They are currently being evaluated in animal studies so that it was primarily reported in vitro. Another advantage of them is reducing immune rejection due to the capability of transplanted autologously. However, those cells have some disadvantages, such as a reduced proliferation and tumorigenic potential to form teratomas in transplanted organs [15, 52-54].

Human IPSCs are used to obtain hair cells and auditory neurons in vitro so that their differentiation is associated with the choice of culture medium and growth factors, activation of fibroblast growth factors signaling pathway, and inhibition of signaling pathway such as Notch signaling to produce otic differentiated cells [55]. The establishment of differentiated otic cells is the expression of several specific markers (PAX8/2, SOX2, and GATA3) in developmental stages as an otic epithelial progenitor. After 4 weeks, these cells can express cell markers like hair cells such as MYOSIN 7A, Espin, ATOH1, and cell markers of an auditory neuron consist of β-tubulin and synapsin [26, 56].

Routes of transplantation of stem cell

Survival and differentiation rates of implanted cells are indirectly dependent on the route of transplantation [7]. Generally, there are two transplantation approaches: local (cochlea) and systemic approaches. The local transplantation aims to deliver cells to the Corti Organ. This procedure is flawless if it is done directly, but it is inaccessible due to the microstructure of this organ [12]. Local implantations are commonly reported in animal studies. Those implantations could be delivering cells into the scala tympani, scala media, modiolus, posterior, or horizontal semicircular ducts using cochleostomy or labyrinthectomy. Recently a study reported delivery of MSCs to the cochlear nerve trunk using the occipital bone approach. This procedure was reported a new successful route without damaging cochlea tissue [18].

The local approach would offer advantages, such as the ability to place cells in the Corti Organ and release of specific factors into the microenvironment of scala media and also higher survival and engraftment rates of stem cells than extra skull transplantation. Disadvantages of this approach can be the risk of injury to cochlear structure, infection, meningitis, and unevaluable complications like vertigo and tinnitus [11, 16, 17, 22, 57, 58].

The results of transplantation of stem cells into the sidewall tissue of the cochlea, the modiolus, or the cochlear nerve showed an increased survival rate of cells and also migration to the canal of Rosenthal. These routes seem more efficient than other local routes such as scala tympani [12, 49, 59].

One of the most significant challenges in stem cell transplantation is potassium-rich endolymph in the cochlea that induces a hostile medium for implanted cells and decreases the survival rate. So rising survival and homing cells were reported by induction of derived factors from connective tissue stroma, such as SDF1 and MCP 1 and MSC with specific receptors [21, 34, 42, 60-62].

The systemic approach can be intravenous transplantation and subarachnoid injection. This approach does not cause direct damage to the cochlea, although the chance of reaching cells to the cochlea is not significant [14]. Intravenous stem cell transplantation needs more numbers of stem cells than other routes of transplantation. A significant part of injected stem cells is trapped in the lung tissue, and only a small number reaches the cochlea tissue [63]. So enough volume is necessary for the injection of stem cells. Theoretically, injection through the vertebral artery is better than peripheral arteries such as the caudal artery (animal tail) due to bypass of the pulmonary circulation. But this procedure is challenging and needs expertise. There are some potential complications such as endolymph disturbance, vertigo, and tinnitus in intravenous transplantation. A study reported that intravenously transplanted stem cells have various distributions in the cochlea, and more cells can be found in the spiral ganglions. It may propose higher permeability of capillaries in spiral ganglion than stria vascularis [14].

A subarachnoid injection is a nonconventional approach in animal studies. The auditory nerve and cortex are floating in CSF and are connected with perilymph, so the transplanted cells can probably be attached around neural fibers and induced functional gain. These advantages include the lower volume of cells in comparison with intravenous injection, passing easily blood-brain barrier and also do not entrap in the pulmonary system [44].

Human umbilical cord blood stem cells

Two main types of stem cell transplantation are autologous and allogenic based on who donates the stem cells. Autologous transplant stem cells are prepared by the patients and used for themselves. An allogeneic transplant is from a person other than the patient. The stem cells for transplant (autologous or allogenic), usually derived from bone marrow, peripheral blood, or umbilical cord blood [64].

Bone marrow is an essential and available source of stem cells used for bone marrow deficiency such as aplastic anemia about 40 years ago. After peripheral blood and bone marrow, the Human Umbilical Cord Blood (HUCB) is introduced as a novel and worthy source for stem cells during recent decades. HUCB is not only a much-enriched source for stem cells, but it also has less immunogenic characteristics and a higher incidence of acute graft-versus-host disease as compared with other sources [65, 66].

Another benefit compared to the bone marrow can be noted as follows: useable in allogeneic transplantation without the need for matching HLA antigen, easy and low-cost preparation, probably accelerated transplantation due to the presence of mesenchymal cells along with other mononuclear cells, high plasticity for nerve tissue repair, presence of molecules and chemical factors, such as neuroprotectants. So even if they do not reach the target tissue, such as the cochlea, these factors will positively affect the damaged tissue [35, 66, 67].

There are abundant mononuclear cells in HUCB, and each one has different functions and behaviors. Those cells could be obtained easily with no injury to the infant or his/her mother, in contrast with embryonic stem cells with their ethical issues. The most important mononuclear cells consist of hematopoietic stem cells, endothelial progenitor cells, immature lymphocytes, monocytes, and mesenchymal stem cells (Figure 1). Because of the low number of mesenchymal cells, the volume of HUCB should be appropriate to obtain the beneficial effects in transplants [65].

The evidence has demonstrated the efficacy of HUB in repairing SNHL in preclinical and clinical studies. Revoltella et al. injected HUCB intravenously to deaf mice (caused by kanamycin treatment and or intense noise) and demonstrated the migration of stem cells in the Corti Organ using histology analysis. They observed morphological recovery in the inner ear of transplanted mice as compared with a control group [68].

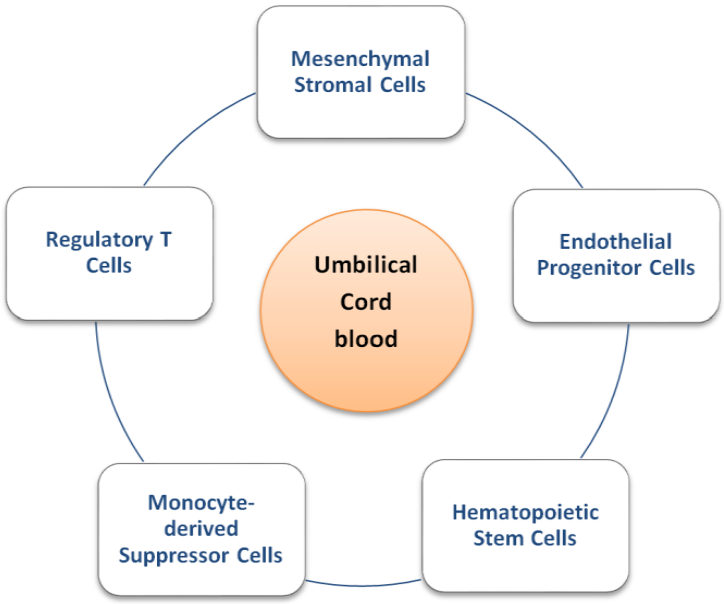

Figure 1. Human umbilical cord blood-derived mononuclear cells

Choi et al. confirmed the positive effect of mesenchymal stem cell-derived HUCB transplanted intravenously in guinea pigs with the SNHL model (application of ouabain and neomycin). They found an improvement of the ABR threshold of up to 40 dB compared to 80-90 dB in the control group that had a saline injection. Also, they showed an increase in hair cells and spiral ganglion cells in the cochlea of transplanted guinea pig [58].

Stem cell therapy on human samples

Several clinical trials tested a single intravenous infusion of umbilical cord blood in children with some nervous system disorders and evaluated its safety and efficiency. Sun et al. showed that children with cerebral palsy who received a high dose of mononuclear cells demonstrated beneficial effects on motor function and brain connectivity [69]. Those improvements can be proposed through paracrine signaling. In the phase 1 study of Dawson, autologous umbilical cord blood was administered in children with autism spectrum disorders. He and his colleagues reported the safety and feasibility of this procedure and also significant behavioral improvements after infusion [70]. Laskowitz et al. investigated the effect of allogeneic HUB in adults with ischemic stroke. They found improvement in the neurological function score along with its safetyness [71].

Table 1. List of registered clinical trials in Cinical Trials.Gov. website

Sponsor/Author	NCT Number	Title	Population	Status	Location
Baumgartner [76]	NCT02038972	Safety of Autologous Umbilical Cord Blood Therapy for Acquired Sensorineural Hearing Loss in Children	Six Weeks to 6 Years (Child)/ all sex	Completed	Florida Hospital, Orlando, Florida, United States
Baumgartner [77]	NCT02616172	Autologous Bone Marrow Harvest and Transplant for Sensorineural Hearing Loss	Two to 6 Years/ all sex	Suspended	Florida Hospital for Children, Orlando, Florida, United States
Baumgartner [78]	NCT01343394	Safety of Autologous Human Umbilical Cord Blood Mononuclear Fraction to Treat Acquired Hearing Loss in Children	Six Weeks to 18 Months (Child)/all sex	Suspended	Children's Memorial Hermann Hospital, Houston, Texas, United States

Mucopolysaccharidosis is an X-linked lysosomal storage disorder in children that affects multiple systems, such as the auditory nervous system. Those children show progressive SNHL. Some studies reported stopped progression of SNHL or improvement of defect due to the effect of stem cell therapy in children with mucopolysaccharidosis I, II related to starting injection [72-74]. Also, in an observational study, significant hearing improvement has been reported in receiving intravenous hematopoietic stem cells from the cord blood [75].

In our literature review, there are currently clinical trials that have been registered in the clinical trials database website (Table 1), and the scientific report of one of those was published in 2018. Baumgartner et al. investigated the effect of autologous umbilical cord blood on 11 children with acquired SNHL. In this clinical trial, all children had moderate to profound hearing loss, and their ages ranged between 5 months to 7 years. They received a single intravenous HUCB with a mononuclear cell dose of 15×10^6 per kg and monitored during infusion. To control the toxicity of the systemic organs, they visited three times in one year after infusion. Children had audiological and neurological assessments before and after infusion (1, 6, 12 months) and brain MRI with DTI technique in 12 months. Audiologic data were obtained using ABR (auditory brainstem response), OAE (otoacoustic emission), audiogram, and tympanometry. The results of this study were hopeful because there were no toxicity and complications. Five out of 11 children showed a decrease in the ABR threshold. They were from 8 patients who had been received a higher dose of cells. Also, there was evidence showing an increase in white matter regions of the primary auditory cortex in fractional anisotropy of MRI [76]. Currently, two clinical trials have registered and have not ended yet [77, 78].

Previously, a case report was published by Lee et al. about autologous bone marrow stem cell treatment in SNHL. They found no significant response in hearing improvement, but in line with Baumgartner's study, they had no complications. It was explainable that patients were adults with SNHL and another with mixed hearing loss [79].

Stem cell therapy for hearing loss in humans (children) is at the beginning. The auditory and other researchers should be aware of the problems and challenges of stem cell therapy in hearing regeneration. One of the future applications of stem cells is the combination therapy of cochlear implantation with stem cells. It is proposed that stem cell-derived neurons can improve the hearing condition. Those probably can produce higher rates of action potential per second [80]. It is necessary to do more research about the effect of electrical stimulation in promoting differentiation and proliferation of transplanted stem cells in cochlea tissue [80].

4. Conclusion

Stem cell transplantation in humans, especially children, requires further studies with larger sample sizes. The time interval between the onset of acquired SNHL and the transplantation of cells can probably influence the results because the fibrous formation in damaged regions may decrease the chance of placing transplanted cells. Although molecular mechanisms and chemical signals underlying auditory electrophysiology have not been fully understood, autologous transplantation had induced relative improvement without serious adverse events.

Future direction

It has been seen that electrical stimuli play a positive role in the differentiation of cells (neurons) using the release of biological factors. Hence acoustic and or electrical stimuli may be helpful in stem cell transplantation of the auditory system. However, more studies are required in responding to challenges and identifying influential factors in transplantation. As well, allogenic transplantation with HUCB should be studied as an alternative for autologous transplantation.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Medical Ethics Committee of Iran University of Medical Sciences, Tehran.

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Authors' contributions

Both authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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