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Title: The Beginning of Stem Cell Therapy in Children with Sensorineural Hearing Loss: A Narrative Review

Running title: Stem Cell Therapy and Sensorineural Hearing Loss

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Abstract

Context:

One of the human desires is to treat children's sensorineural hearing loss with stem cell transplantation. Preclinical studies have been performed in this field and the stem cell types have been tested and achieved relative improvement.

Evidence Acquisition:

This narrative review has been prepared about hearing regeneration with stem cell transplantation. The articles with Full-text and English Language have been searched in PubMed, Scopus, and google scholar from 2000 through 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 in terms of the safety of the method and the positive effect on hearing.

Conclusions:

Autologous stem cell transplantation had induced noticeably relative improvement without serious adverse events in children with acquired sensorineural hearing loss. to obtain more evidence, requires further studies with larger sample sizes and population groups.

Keywords: Children, Sensorineural hearing loss, Stem cell

Context:

The prevalence of hearing loss is about 5 percent (466 million people) in the world that almost 34 million belongs to children. World health organization(WHO) estimated to reach about 900 million people will involve with hearing loss by 2050 [1, 2]. Sensorineural hearing loss (SNHL) is a type of hearing loss that can be related to sensory hair cells' damage of the afferent nerve pathway. The severity of SNHL can be mild to profound. The moderate and up of it certainly requires therapeutic management, otherwise, it can be induced to defects of speech and communication skills. Cochlear implantation (CI) is the only useful treatment for profound hearing loss, which is a metal implant placed inside the cochlea. CI is not satisfactory in children with auditory neuropathy and also is costly for patients and the health system. Stem cell therapy could be a novel therapeutic approach in children with moderate to profound SNHL[3] with considering the effect of stem cell transplantation in some neurological diseases. The mammalian body tissues, including humans, have stem cells (SCs) that remain after birth that can be useful in regeneration medicine for some diseases. There is no evidence of the existence of SCs in nervous cells and sensory cells of the cochlea after birth. [4-6].

Some studies suggest exciting hematopoietic stem cells from bone marrow in the mature inner ear that can be differentiated into fibrocytes or resident macrophages, but there is no data about developing them as hair cells[7-9]. However, it is unknown to activated procedures for changing the fate. Therefore, it is necessary for an external source of stem cell as an alternative strategy. Some supporting cells in the cochlea have capable to transdifferentiate to hair cells if those lie in 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. The studies have elucidated that some molecular agents and fibroblast growth factors can be effective in inner ear development. The otic progenitor cells were produced from hSCs (human stem cells) under special conditions in-vitro that these cells were differentiated to hair cell-like cells and auditory neuron-like cells[16, 17]. Experimental studies have reported the recovery of 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 that used for hearing regeneration, as well as recent advances for the therapy of SNHL in children.

Evidence Acquisition:

In this narrative review article, we investigated the current 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 ((sensory neural hearing loss OR SNHL) AND stem cell) by the English Language. After the abstract screening, the full text of related studies was reviewed and studies were about stem cell transplantation in vestibular system and meeting abstracts, editorials, letters, and commentaries 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.

Results:

The types of Stem cell in hearing regeneration:

Many studies in-vivo and in-vitro 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].

Overall, 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]. Each of these cells can be shown 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 didn't have enough integrated cells and synapses competent in the microstructure of

Corti organ[16, 27-29]. These differentiated cells to hair cells had not electrophysiologically maturated and developed, perhaps the presence of acoustic stimuli can be effective in the maturation process[25].

ESCs are prepared from mammalian embryonic blastocysts that have unlimited reproducibility and could differentiate into any of the three embryonic layers (ectoderm, endoderm, or mesoderm). There are shortcomings for using the ESCs that including of ethical issues due to the destruction of a viable embryo, high probability of transplantation rejection, tumorigenesis risk after years of transplantation[24, 30, 31].

Adult stem cells are a common sample for stem cell transplantation that is 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, less moral problems, and low risk of rejection compared to ESCs [32]. The most common adult stem cells that were used for hearing regeneration are mesenchymal stem cells(MSCs). MSCs 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, platelet-derived growth from damaged tissue[10, 33-35]. MSCs in comparison with other stem cells that have less expensive, and easier preparation, and also tumorigenesis risk. It has been reported that those cells can convert to neural cells due to neuroprotective property[36, 37]. Those can be subpopulations from various sources such as bone marrow, peripheral blood, umbilical cord, fat tissue, and other tissue, that the bone marrow is the most important source[33, 38].

Some preclinical studies reported the expression of specific cellular markers related to hair cell 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 be had 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 Corti organ, spiral ganglion neurons, or fibrocytes [14, 16, 21, 42-44]. An interesting point about other properties of those cells, the presence of mechanical stimulation sensitive receptors is in the surface of MSC. In some studies, it has been observed that proliferation and differentiation of MSC have been increased by the stimulation of these receptors with sound stimuli[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 is an appropriate source for the preparation of those cells. The neural stem cells have specific receptors that bind with probable chemical factors secreted from Schwann cells of the damaged auditory nerve[48, 49].

The third group of stem cells is induced pluripotent stem cells(IPSCs) that can be derived from each somatic tissue in vitro and then are reprogrammed to obtain the ability 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 mostly reported in vitro. Another advantage of them is reducing immune rejection due to the capability of transplanted autologously. Those have some disadvantages such as a reduced proliferation, tumorigenic potential to form teratomas in transplanted organs[15, 52-54]. Human IPSCs were used to obtain hair cells and auditory neurons in-vitro that differentiation of them are related to 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 otic differentiated cells is the expression of several specific markers (PAX 8, 2, SOX2, and GATA3) in developmental stages as an otic epithelial progenitor. These cells can express after 4 weeks of cell markers of like hair cells such as MYOSIN 7A, Espin, ATOH1, and cell markers of an auditory neuron consist of β Tubulin, 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 consisted of local (cochlea) and systemic approaches. The aim of local transplantation is delivering of cells to the Corti organ. This was very perfect if it was done directly, but it is inaccessible due to the microstructure of this organ [12]. Local implantations are commonly reported in animal studies. Those could be the delivery of 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 that this was reported a new successful route without damaging to cochlea tissue [18]. The local approach would offer advantages, such as the ability to placing of cells in the Corti organ probability due to the 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 Rosenthal's canal. These routes seem more efficient than other local routes such as scala tympani[12, 49, 59].

One of the most major 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 together MSC with specific receptors[21, 34, 42, 60-62].

The systemic approach can be intravenous transplantation and subarachnoid injection. Its advantage is that does not cause direct damage to the cochlea, against the reaching chance of 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 into the lung tissue and only a small number reaches the cochlea tissue[63]. So it is a necessary enough volume 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 the pulmonary circulation, but it is no easy 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 distribution in the cochlea and more number cells can be found in the spiral ganglions. It proposes probably 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 float in CSF and relate with perilymph, so the transplanted cells can probably be attached around neural fibers and induced functional gain. These advantages include requiring a lower volume of cells in comparison with intravenous injection, the cells pass easily blood-brain barrier and also don't entrap in the pulmonary system[44].

Human umbilical cord blood stem cells:

Two main types of stem cell transplantation named autologous and allogenic based on who donates the stem cells. Autologous transplant, stem cells are prepared from the patient and used for herself or himself. 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 important and available source of stem cells that it had been 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 worthy source for stem cells during recent decades. HUCB is not only a much-enriched source for stem cells but also it has less immunogenic characteristics and 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 of 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 that even if they do not reach the target tissue such as the cochlea, these factors will have a positive effect on 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 ethical issues. The most important mononuclear cells consist of hematopoietic stem cells, endothelial progenitor cells, immature lymphocytes, monocytes, and mesenchymal stem cells (figure1). According to low numbers of mesenchymal cells, the volume of HUCB should be appropriate to obtain 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 mice with deaf 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]. Choi et al confirmed the positive effect of mesenchymal stem cell-derived HUCB that was transplanted intravenously in guinea pigs with the SNHL model (application of ouabain and neomycin). They found improvement of the ABR threshold of up to 40 dB in comparison with 80-90 dB in a control group that had a saline injection and 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 the safety and efficiency. Sun et al. showed 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's Dawson, autologous umbilical cord blood was administered in children with autism spectrum disorders. He and his colleagues reported the safety and feasibility of it and also significantly 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 the safety[71].

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 arrested progression of SNHL or improvement of defect due to effect of stem cell therapy in children with mucopolysaccharidosis I, II that is related to the time of starting injection[72-74]. Also, in an observational study, significant hearing improvement has been reported in receiving intravenous hematopoietic stem cells from 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 eleven children with acquired SNHL. In this clinical trial, all children had hearing loss with moderate to profound degree and the aged was almost 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 also 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 findings from toxicity and complications. Five from 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 from an increase in white matter regions of the primary auditory cortex in fractional anisotropy of MRI[76]. Currently, two clinical trials have registered and haven't ended yet[77, 78].

Previously, a case report was published by Lee and his colleagues about autologous bone marrow stem cell treatment in SNHL. They found no significant response in hearing improvement, but in line with Baumgartner's study 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 researchers 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 combination therapy cochlear implantation with stem cells. It is proposed of stem cell-derived neurons can improve the hearing condition. Those probably can produce higher rates of action potential per second[80]. It is necessary for doing more research about the effect of electrical stimulation in promoting differentiation and proliferation of transplanted stem cells in cochlea tissue [80].

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 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 been not fully understood. However autologous transplantation had induced noticeably relative improvement without serious adverse events.

Future direction:

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

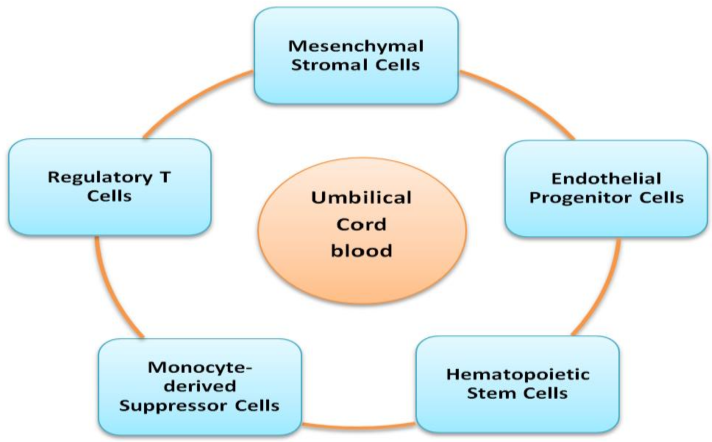

Figure1: Human umbilical cord blood-derived mononuclear cells

Table 1: List of registered clinical trials in clinical trials.gov. Website.

Sponsor/Author	NCT Number	Title	Population	Status	Location	URL
Baumgartner J	NCT02038972	Safety of Autologous Umbilical Cord Blood Therapy for Acquired Sensorineural Hearing Loss in Children	6 Weeks to 6 Years (Child)/ all sex	Completed	Florida Hospital, Orlando, Florida, United States	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6233943/
Baumgartner J	NCT02616172	Autologous Bone Marrow Harvest and Transplant for Sensorineural Hearing Loss	2 Years to 6 Years/ all sex	Suspended	Florida Hospital for Children, Orlando, Florida, United States	https://clinicaltrials.gov/ct2/show/NCT02616172?term=stem+cell&cond=hearing&draw=2&rank=4
Baumgartner J	NCT01343394	Safety of Autologous Human Umbilical Cord Blood Mononuclear Fraction to Treat Acquired Hearing Loss in Children	6 Weeks to 18 Months (Child)/all sex	Suspended	Children's Memorial Hermann Hospital, Houston, Texas, United States	https://clinicaltrials.gov/ct2/show/NCT01343394?term=stem+cell&cond=hearing&draw=2&rank=2

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