

Review Article

Stem cell therapy for sensorineural hearing loss: a narrative review

Santosh K. Swain*

Department of Otorhinolaryngology and Head and Neck Surgery, All India Institute of Medical Sciences, Sijua, Patrapada, Bhubaneswar, Odisha, India

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*Correspondence:

Dr. Santosh K. Swain,

E-mail: santoshvoltaire@yahoo.co.in

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ABSTRACT

Transplanting neural stem cells has drawn a lot of interest as a novel therapeutic approach for replacing specific cells that have been harmed by disorders like neurodegenerative diseases. Neural stem cell transplantation has a significant therapeutic impact on cell activation and regeneration as well as the restoration of damaged neurons in many organs. As stem cell research advances, stem cell therapy will become more important in treating inner ear diseases including sensorineural hearing loss. The invasive surgical procedure may result in severe hearing loss because of the unique structure of the cochlea. Therefore, several methods are chosen for neural stem cell implantation depending on the conditions and goals of the treatment. The methods for stimulating endogenous and exogenous stem cell differentiation in the inner ear are discussed in this review article. Although stem cell therapy still has many drawbacks, its potential to treat hearing loss has been widely acknowledged. This review attempts to provide a thorough overview of stem cell therapy for sensorineural hearing loss (SNHL), the difficulties encountered, and possible future prospects in this field by combining recent research and innovation.

Keywords: Sensorineural hearing loss, Stem cell therapy, Neural stem cells, Cochlea

INTRODUCTION

Sensorineural hearing loss (SNHL) is a common hearing dysfunction that occurs primarily due to defect in inner ear or auditory nerve.¹ SNHL has several causes such as genetic etiology, age related degeneration, noise exposure, ototoxicity, and various diseases.² The pathogenesis of SNHL is mainly involves damage to or death of hair cells of the cochlea.² Sound waves are converted by the cochlear hair cells into electrical signals, which are then sent to the brain by the auditory nerve.³ Mammals' inner hair cells cannot normally regrow after damage, in contrast to birds.² So, the treatment is often challenging for restoring the normal hearing. Hearing aids and various implantable hearing devices, such cochlear implants, are effective in treating or rehabilitating severe to profound sensorineural hearing loss.⁴ Although these treatments are widely recognized and accessible, not every patient will benefit from them. Even some patients find these devices unsatisfactory. Trials of stimulating regeneration or trans-

differentiation of these stem cells using various techniques have drawn attention to their potential use in afflicted patients since the discovery of stem cells in the human cochlea.⁵ The aim of this review article is to discuss overview of stem cell therapy for SNHL, the difficulties encountered, and possible future prospects in this field by combining recent research and innovation.

METHODS OF LITERATURE SEARCH

A search was conducted for research articles on the stem cell therapy in SNHL. This began with searching online databases such as Google Scholar, Scopus, PubMed, and Medline. A search strategy was developed following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Articles were initially screened by their titles to determine eligibility, followed by a thorough review of each abstract to ensure they met the inclusion criteria. The search approach found published article abstracts, and citations were used to

manually find more research publications. The review evaluated the suitability of incorporating observational studies, comparative studies, case series, case reports, and randomized controlled trials. A total of 68 articles (24 case reports, 16 case series, and 28 original articles) were found across various databases, with 41 being included in this review (Figure 1). This article discusses the prevalence of sensorineural hearing loss, stem cells, cochlea as a site for stem cell implantation, neural stem cell therapy, endogenous and exogenous stem cells for hearing restoration, methods of stem cell therapy, challenges, and future direction of stem cell therapy in sensorineural hearing loss. treatment.

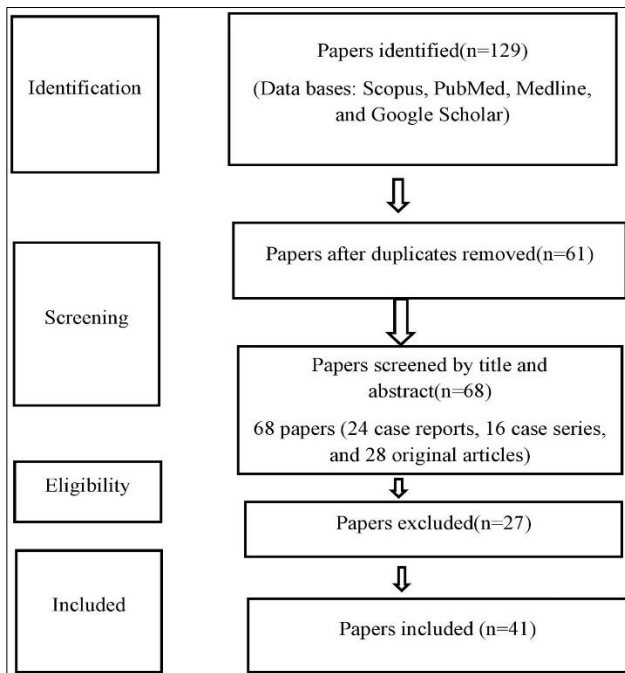


Figure 1: Methods of literature search.

PREVALENCE

Hearing loss is a global health related problem affecting millions of populations. SNHL is one of the most common hearing disorder globally. Sensorineural hearing loss affects about 270 million people worldwide. In newborns, the frequency of SNHL is 2/1000; in children between the ages of 3 and 17, it is 5/1000; in adults between the ages of 65 and 74, it is 33%; and in population over the age of 85 years, it is approximately 50%.⁶ Another study reported, SNHL affects 1.59 billion people, accounting for 20.3% of the total population, with the lives of about a quarter of those being seriously affected.⁷ The impact of SNHL on patients is profound and affects communications and quality of life. SNHL can also lead to social isolation, emotional problems, and reduced cognitive function, particularly affects elderly population.⁸

So, finding an effective treatment to restore hearing loss is a challenging for clinicians and researchers.

SENSORINEURAL HEARING LOSS

SNHL occurs due to lesions in the auditory pathway, including cochlea of the inner ear and auditory nerve.⁹ Sensorineural hearing impairment is caused by a reduction of auditory input to the brain, which is brought on by the less of hair cells of cochlea.¹⁰ Peripheral auditory signals are transmitted via spiral ganglion neurons and cochlear hair cells.¹¹ The cochlea's hair cells release neurotransmitters to the spiral ganglion cells, which subsequently send signals to the auditory center, upon exposure to the mechanical pressure of sound waves.¹¹ Damage to the central auditory system, auditory nerve, or inner ear results in SNHL.¹¹ Damage to hair cells, loss of connections between neurons and hair cells, and neuronal degeneration are the main causes of SNHL.¹² Sensorineural deafness is caused by irreversible cochlear hair cell loss and destruction. New treatments for SNHL may be made possible by promoting hair cell regeneration to some degree through the use of stem cells and gene therapy techniques.¹³ The scientific basis of stem cell therapy is based on the plasticity of stem cells which enables interventions to target specific mechanisms of cochlear hair cells.¹³ Nowadays, replacing damaged hair cells and spiral ganglion neurons as well as inducing stem cell differentiation are becoming more and more viable treatment options for hearing regeneration.¹³

COCHLEA AS SITE OF STEM CELL THERAPY

Cochlea is present in petrous part of the temporal bone, a deep inside the skull.¹⁴ It has a very complex structure and harbours several types of cells.¹⁴ The different types of cells or different cochlear areas can be targeted for stem cells applications. If hearing loss is due to involvement of hair cells, stem cells are targeted to hair cells.¹³ The lateral cochlear wall should be the target if pathology there is the cause of hearing loss.¹⁵ Hair cells and nerve fibers should be the primary targets for stem cell therapy as almost all hearing loss, with the exception of some caused by genetics, is linked to their participation.¹³ Stem cell therapy may be used to treat diseases that have histological abnormalities at the cochlea's lateral wall, which is made up of the spiral ligament and stria vascularis.⁵ Although the spiral ganglion neurons can be a target for stem cell therapy in hearing loss, however hearing loss cannot be restored with an intact spiral ganglion neuron only.¹⁶ Since hair cells play a role in the initial or terminal structure of hearing, an underlying hair cell issue should still be taken into consideration in cases of hearing loss where spiral ganglion neuronal loss and nerve fiber issues have been identified.¹⁷

STEM CELLS

Stem cells are produced by multicellular organisms and can originate from adult tissues or the embryo.¹⁷ Stem cells can differentiate into any kind of specialized animal tissue in a developing embryo. They can also be employed to exchange specialized cells and sustain extra turnover of

regenerative organs, such as the skin, blood, gut, and the body's repair system in adult organs.¹⁸ The undifferentiated cells, also known as pluripotent stem cells, can differentiate into many specialized cell types and give rise to three germinal layers, including ectoderm, mesoderm, and endoderm. Through multiple cycles of mitotic cell division, these cells possess an infinite capacity for self-renewal.¹⁹ These characteristics of stem cells suggest a range of possible clinical uses, including regenerative medicine, drug development, and recombinant protein therapy.²⁰ The inner cell mass of the blastula between days five and eight of the biological process was the best source of pluripotent stem cells.²¹ Human or mouse cells can be genetically reprogrammed to produce pluripotent stem cells, which are similar to embryonic stem cells. There is no future spontaneous hair cell regeneration since the organs of Corti are post-mitotic at birth in mammals. Between 23 and 50 percent of SNHL in children are caused by genetic abnormalities (Connexin 26 mutant deafness, Lange-Nielson syndrome, Pendred syndrome, Usher syndrome, and Waardenburg syndrome).²² SNHL, which is frequently caused by premature birth, sickness during or after delivery, exposure to loud noises, or use of ototoxic medicines, affects the remaining newborns and children.²² In order to reduce the symptoms of SNHL, current treatments, such as cochlear implants or hearing aids, try to increase the hair cells that survive after the injury to the organ of Corti.²³ The impact of cochlear implants is limited by the loss of sensory hair cells in the organ of Corti.²⁴

NEURAL STEM CELLS THERAPY

Neural stem cell therapy has become a cutting-edge technology for tissue regeneration. Strong proliferation and differentiation potential are characteristics of neural stem cells. It is possible to encourage neural stem cells to differentiate into various nerve cells, including oligodendrocytes, neurons, and astrocytes.²⁵ Therefore, neural stem cells can be utilized as a crucial way to replace certain cells that have been harmed by diseases like neurodegenerative diseases, brain injuries, and so on. Depending on where they come from, neural stem cells can be divided into neural stem cells and allogenic neural stem cells. Neural stem cells can be classified as adult neural stem cells, non-neural tissue derived neural stem cells, and embryonic stem cell derived neural stem cells based on growth stages and various tissue sources.²⁶ Neural stem cells have three main therapeutic mechanisms: first, they gather at the site of injury, proliferate, and differentiate into specific cells to restore the function of original tissues; second, they secrete pertinent nutritional factors to enhance the regeneration and recovery of damaged cells; and third, they improve or establish synaptic connections between neural cells and restore nerve conduction pathways. According to a study, neural stem cell replacement therapy has significantly improved the treatment of some neurodegenerative disorders, such as Parkinson's disease and Huntington's disease.²⁷ In a damaged spinal cord, the implanted neural stem cells can thrive. In order to reconstruct the innervation of the

voluntary muscles, these neural stem cells not only replace missing motor neurons but also function as a neuronal relay, creating connections between regenerated axons and between their own axons and host axons.²⁸ In adult ischemic stroke and neuronal ischemic hypoxic encephalopathy, neural stem cell implantation can also lessen brain damage.

Endogenous stem cells for regeneration of hearing

The greater epithelial ridge, lesser epithelial ridge, organ of Corti, vestibular sensory epithelium, and semicircular canals are the locations of the inner ear stem cells in the cochlea and vestibule.²⁹ After being cultured for a while, the neural stem cells are injected into the cochlea through the cochlear sidewall, where they can travel to the region of the cochlea axis where spiral ganglia are dispersed.³⁰ This method is accurate, efficient, and causes very little trauma.

Exogenous stem cells for regeneration of hearing

Many studies have attempted to restore inner ear cells by implanting neural stem cells due to the small amount of stem cells that are currently present in the inner ear and the uncertainty surrounding the mechanism of inner ear cell renewal.³¹ Neural stem cells may develop into functional auditory neurons, according to one study.³² Neural precursor cells, ganglion cells, inner ear stem cells or precursor cells, immortalized auditory neuroblasts, embryonic stem cells and their derived stem cells, and bone marrow stromal cells treated with sonic hedgehog (Shh) and retinoic acid.³³

METHODS OF NEURAL STEM CELL IMPLANTATION IN THE COCHLEA

The appropriate pathway from perilymph, endolymph, cochlear axis, auditory nerve, cochlear lateral wall, and so forth can be chosen by implanting stem cells into the cochlea.³⁴ Round window and semicircular canal injections are part of the perilymph path, while cochlear duct injections are part of the endolymph system.³⁵ In one study, neural stem cells were cultured for a while before being injected into the cochlea through the cochlear sidewall. This allowed the cells to move to the region of the cochlea axis that contained spiral ganglia.³⁶ This method is accurate, efficient, and causes very little trauma. Depending on the circumstances and goals of the treatment, many techniques are used to implant the neural stem cells. Detection is mostly dependent on appearance, protein expression, and genetic markers to ascertain whether neural stem cells are successfully differentiated into target cells after implantation in the cochlea. To determine whether the newly generated hair cells following stem cell implantation have the traits of normal hair cells, the detection may be based on the detection of particular expression genes (MYO7A, BRN3A, and ATHO1), auditory receptors, mechanical energy to electrical energy transformation, and hair cell

electrophysiological activity.³⁷ The mechanism of neural stem cell transplantation for restoration of hearing loss is given in Figure 2.

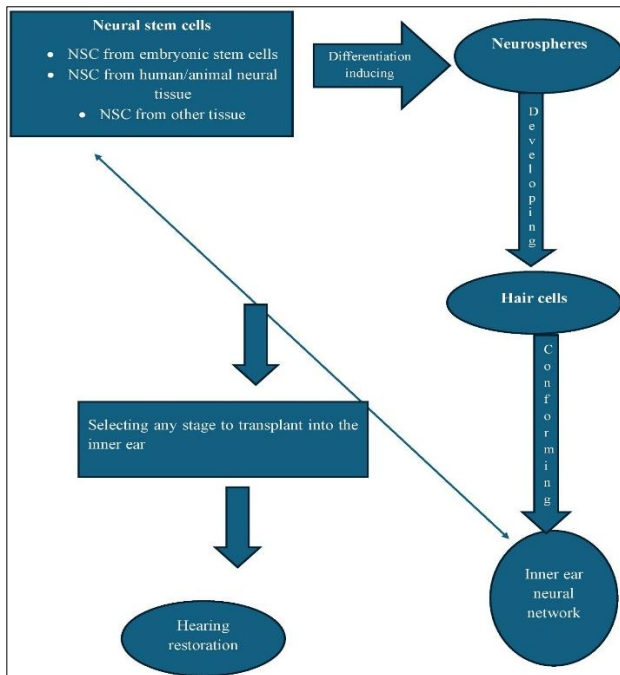


Figure 2: Mechanism of neural stem cell transplantation for restoration of hearing loss.

CHALLENGES IN STEM CELL THERAPY IN SNHL

Stem cell therapy for SNHL faces significant challenges for delivering stem cells safely into inner ear, achieving precise differentiation into hair cells, neural cells, and ensuring long-term survival in hostile environment of the cochlea. The important hurdles include the risk of tumor occurrence, navigating the difficult anatomical access, and overcoming the limited, functional integration of new cells.³⁶ Even if the cells survive, they should properly connect with existing neural networks to transmit sound, which is difficult in presence of scar tissue.³⁶ There are no reliable blood biomarkers for SNHL, making it difficult to detect the exact progress of the stem cell therapy. The cochlea has a high potassium environment that is toxic to many transplanted cells, so stem cells may fail to survive in the endolymph.³⁸

FUTURE DIRECTIONS OF STEM CELL THERAPY IN SNHL

At present, stem cell therapy for SNHL is still in the preliminary stage and preclinical trials stages. However, there are some positive results have been achieved for restoring hearing loss with stem cell treatment. Some studies have proven that specific types of stem cells able to differentiate into hair cell like cells in the injured cochlea, promising to restore or improve hearing.^{39,40} These investigations not only provide fresh perspectives

on the pathology of cochlear hair cell regeneration mechanisms, but they also set the stage for the development of innovative treatments for SNHL. With continued advancements in stem cell science and related biomedical engineering, neural stem cell therapy is anticipated to become one of the most successful treatments for SNHL in the future. This requires more than just a thorough analysis of neural stem cell type, source, safety, and efficacy. Stem cell technology holds great promise for treating SNHL in the future with further research and innovation. Furthermore, more accurate and customized approaches to treating SNHL are provided by 3D bioprinting technology associated with neural stem cell therapy, gene editing technology, and enhanced drug delivery systems.⁴¹ By carefully controlling particular genes or signaling pathways, this method can improve the efficacy and safety of stem cell therapy in addition to encouraging the targeted differentiation and tissue regeneration of stem cells. This field still confronts many obstacles despite the promising application of stem cell technology, which offers novel solutions that are not possible with conventional treatments. These issues, which call for ongoing research and development, include long-term stability, precise regulation of cell differentiation, and possible tumor danger. The use of stem cell technology in regenerative medicine will grow along with technological advancements and a better comprehension of stem cell behaviour, creating new avenues for SNHL clinical practice and future medical research.

CONCLUSION

Many barriers prevent stem cell therapy from being used to treat sensorineural hearing loss, yet it is possible to replace or repair organs and tissues that lack regenerative ability. Human stem cell-derived auditory progenitor cells were successfully inserted into the injured cochlea, demonstrating the stem cells' enormous potential to restore hearing. The ability of human stem cells to support cochlear restoration in real-world applications is demonstrated by experimental validation in animal models, which also establishes a strong basis for the advancement of stem cell-based therapeutic approaches.

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