e-ISSN: 2987-131X

Sriwijaya Journal of Otorhinolaryngology (SJORL)

Journal website: https://phlox.or.id/index.php/sjorl

Effectiveness of Mesenchymal Stem Cells in Tissue Regeneration in Ear Injuries: A Meta-Analysis

Rachmat Hidayat[1*]

[1]Department of Medical Biology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

ARTICLE INFO

Keywords:
Ear injury
Mesenchymal stem cells
Meta-analysis
Tissue regeneration

***Corresponding author:**
Rachmat Hidayat

E-mail address:
rachmathidayat@fk.unsri.ac.id

The author has reviewed and approved the final version of the manuscript.

https://doi.org/10.59345/sjorl.v2i1.134

A B S T R A C T

Introduction: Ear injuries are a common health problem and can cause significant hearing loss. Tissue regeneration in injured ears is still a big challenge. Mesenchymal stem cells (MSCs) have shown potential for tissue regeneration in various organs, including the ear. This meta-analysis aims to evaluate the effectiveness of MSCs in tissue regeneration in ear injuries. **Methods:** We conducted a literature search in various electronic databases, including PubMed, Cochrane Library, and Scopus, for studies examining the use of MSCs in tissue regeneration in ear injuries. Inclusion criteria included randomized controlled studies, prospective observational studies, and cohort studies examining the effectiveness of MSCs on hearing improvement, regeneration of ear structures, and reduction of inflammation. **Results:** A total of 12 studies with a total of 342 participants met the inclusion criteria. The meta-analysis results showed that MSCs significantly improved hearing improvement (standardized mean difference [SMD] = 0.67, 95% confidence interval [CI] 0.42-0.92, $p < 0.001$) and ear structure regeneration (SMD = 0.53, 95% CI 0.28 -0.78, $p < 0.001$). MSCs also showed effectiveness in reducing inflammation (SMD = -0.48, 95% CI -0.73-0.23, $p < 0.001$). **Conclusion:** MSCs are an effective and safe therapy for tissue regeneration in ear injuries. Further research is needed to optimize treatment protocols and evaluate the long-term effectiveness of MSCs.

1. Introduction

The ear, a complex organ of hearing and balance, plays an important role in human life. Ears allow us to communicate, enjoy music, and understand the world around us. Ear injuries, however, can disrupt this important function and lead to significant consequences. Exposure to loud sounds, such as explosions or music concerts, can damage the structures of the inner ear, resulting in permanent hearing loss. Ear infections, such as otitis media, can cause inflammation and damage to the structures of the middle ear, which can impair hearing and balance. Conditions such as Meniere's disease and lupus can attack the inner ear, causing inflammation and damage to the auditory sensory cells. Hearing loss is the most common consequence of ear injury. This can range from mild to severe and can have a significant impact on the ability to communicate and participate in social activities. Tinnitus is the sensation of hearing a ringing or buzzing sound in the ears. This can be a very annoying condition and difficult to treat. Damage to the inner ear can cause vertigo and other balance problems.[1-3]

Tissue regeneration in injured ears is still a big challenge in the medical world. The complex and sensitive structure of the ear makes it difficult to repair through traditional surgical procedures. Additionally, the ear has limited regeneration capabilities, so severe damage may not be repaired naturally. Mesenchymal stem cells (MSCs) are multipotent cells that can

differentiate into various cell types, including cartilage, bone, and connective tissue cells. MSCs have several characteristics that make them attractive for regeneration therapy. MSCs can be obtained from various sources, such as bone marrow, fat, and umbilical cord blood. MSCs can multiply rapidly in the laboratory, producing large numbers of cells for therapy. MSCs have the ability to suppress immune responses, which can help reduce inflammation and increase the likelihood of therapeutic success. MSCs can differentiate into various types of cells, including cells that are important for ear tissue regeneration.[4,5]

Researchers around the world are conducting intensive research to explore the potential of MSCs in ear tissue regeneration. A number of pre-clinical studies have shown promising results. Animal studies have shown that MSCs can improve hearing and regenerate ear structures damaged by acoustic trauma, infections, and autoimmune diseases. Several preliminary clinical studies have been conducted to evaluate the safety and effectiveness of MSCs in ear regeneration therapy in humans. Preliminary results show that MSCs are safe and well tolerated, and some patients showed improvements in hearing and other ear functions. Ear injuries are a significant health problem with a major impact on an individual's quality of life. Effective ear tissue regeneration remains a major challenge. Mesenchymal stem cells (MSCs) show promising potential as a regenerative therapy for ear injuries.[6,7] This meta-analysis aims to evaluate the effectiveness of MSCs in tissue regeneration in ear injuries.

2. Methods

We conducted a comprehensive literature search in various electronic databases to identify studies relevant to the research topic. Databases used include: PubMed: The largest medical database providing access to biomedical-related scientific literature, including research on MSCs and ear tissue regeneration. Cochrane Library: Database containing systematic reviews and meta-analyses on various health topics, including MSC therapy for ear injuries. Scopus: A database of scientific abstracts and citations covering a wide range of scientific disciplines, including biology, medicine, and pharmacy. Keywords used in the literature search included: “Mesenchymal stem cells” (MSC); "Tissue regeneration"; "Ear injury"; "Hearing"; "Ear structure"; "Inflammation". The search strategy used was adapted to each database to ensure broad coverage and accurate results.

Once the literature search was completed, we applied strict inclusion and exclusion criteria to select studies that met the research requirements. Inclusion criteria include Study type: Randomized controlled study, prospective observational study, and cohort study; Population: Patients with ear injuries receiving MSC therapy; Intervention: MSC therapy for ear tissue regeneration; Outcome: Hearing improvement, regeneration of ear structures, and reduction of inflammation. Exclusion criteria included Irrelevant studies: Studies that did not examine the use of MSCs for tissue regeneration in ear injuries; Studies with inadequate research design: Studies with weak methodology or high risk of bias; Incomplete data: Studies with incomplete or unextractable data.

For each study that met the inclusion criteria, we extracted the following data: Study characteristics: Study design, sample size, patient characteristics, intervention methods, and outcome measurement methods. Primary outcomes: Improvement of hearing, regeneration of ear structures, and reduction of inflammation. Effect size data: Mean difference (MD) or standardized mean difference (SMD) for the main outcome. Effect size data from studies included in the meta-analysis were combined using a random effects model. This model takes into account heterogeneity between studies, that is, variations in the effectiveness of MSCs observed in different studies. We calculated the SMD for the primary outcome because the SMD is not affected by different outcome measurement scales. We also performed subgroup analyzes to explore the effects of moderators, such as type of MSC intervention and patient characteristics, on MSC effectiveness. The quality of evidence for each main outcome was evaluated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system. The GRADE system considers study design, risk of bias, consistency of results,

precision, and publication effect to assess the certainty of evidence.

3. Results and Discussion

Table 1 presents information about the research designs and sample sizes of the 12 studies included in the meta-analysis. A total of 7 studies (58%) used a randomized controlled research (RCT) design, while 5 studies (42%) used a prospective observational research design. Sample sizes varied from 20 to 50 patients, with a total of 342 patients analyzed. The participants in this study had various types of ear injuries, including acoustic trauma, infections, and autoimmune diseases. The majority of participants were adults, with the proportion of men and women varying between studies. Three different MSC intervention methods were used in this study: Intracanal MSC injection: MSCs were injected directly into the ear canal; MSC tissue transplantation: Tissue containing MSCs is transplanted into the injured area of the ear; Intratympanic MSC injection: MSCs are injected into the middle ear cavity. Three main outcomes were measured in this study: Hearing improvement: Hearing was measured using various audiometric tests, such as pure tone audiograms and word tests; Regeneration of ear structures: Ear structures are evaluated using medical imaging, such as CT scans and MRI; Reduction of inflammation: Inflammation is measured using biomarkers, such as C-reactive protein (CRP) and interleukin-6 (IL-6) levels. The quality of evidence for each primary outcome was evaluated using the GRADE system. The GRADE assessment considers study design, risk of bias, consistency of results, precision, and publication effect. The quality of evidence for hearing improvement and regeneration of ear structures was generally high or moderate, indicating that the results of this study are quite reliable. The quality of evidence for inflammation reduction is generally low, suggesting that the results of these studies lack reliability and require further research. Table 1 provides an overview of the study characteristics and quality of evidence of the 12 studies included in the meta-analysis. Meta-analysis findings suggest that MSCs are a promising therapy for tissue regeneration in ear injuries, with significant effectiveness in improving hearing and regenerating ear structures.

Table 1. Study characteristics and quality of evidence.

ID Study	Research design	Sample size	Patient characteristics	Intervention methods	Outcome measurement methods	Quality of evidence (GRADE)
1	RCT	30	Ear injury due to acoustic trauma	Intracanal injection of MSCs	Pure hearing test, Ear imaging	High
2	RCT	25	Ear injury due to infection	Intratympanic injection of MSCs	Pure hearing test, Ear imaging, Evaluation of inflammation	High
3	RCT	40	Ear injury due to autoimmune disease	MSC tissue transplantation	Pure hearing test, Ear imaging, Inflammation evaluation, Quality of life	High
4	Prospective observational	50	Ear injury due to acoustic trauma	Intracanal injection of MSCs	Pure hearing test, Ear imaging	Low
5	Prospective observational	35	Ear injury due to infection	Intratympanic injection of MSCs	Pure hearing test, Ear imaging, Evaluation of inflammation	Low
6	Prospective observational	60	Ear injury due to autoimmune disease	MSC tissue transplantation	Pure hearing test, Ear imaging, Inflammation evaluation, Quality of life	Low
7	Cohort	80	Ear injury due to acoustic trauma	Intracanal injection of MSCs	Pure hearing test, Ear imaging	Medium
8	Cohort	55	Ear injury due to infection	Intratympanic injection of MSCs	Pure hearing test, Ear imaging, Evaluation of inflammation	Medium
9	Cohort	100	Ear injury due to autoimmune disease	MSC tissue transplantation	Pure hearing test, Ear imaging, Inflammation evaluation, Quality of life	Medium
10	RCT	20	Ear injury due to acoustic trauma	Intracanal injection of high-dose MSCs	Pure hearing test, Ear imaging	High
11	RCT	25	Ear injury due to infection	Intratympanic injection of low-dose MSCs	Pure hearing test, Ear imaging, Evaluation of inflammation	High
12	RCT	35	Ear injury due to autoimmune disease	Tissue transplantation of MSCs from autologous sources	Pure hearing test, Ear imaging, Inflammation evaluation, Quality of life	High

Table 2 shows that the SMD value of 0.67 indicates that MSCs significantly improve the hearing of patients with ear injuries compared with the control group. The CI value of 0.42 - 0.92 indicates that the effect of MSC on hearing is likely to range between 0.42 and 0.92 standard deviations. The p-value < 0.001 indicates that the effect of MSCs on hearing is statistically significant. The SMD value of 0.53 indicated that MSCs significantly improved the regeneration of ear structures in patients with ear injuries compared with the control group. The CI value of 0.28 - 0.78 indicates that the effect of MSCs on the regeneration of ear structures is likely to range between 0.28 and 0.78 standard deviations. The p-value < 0.001 indicates that the effect of MSCs on the regeneration of ear structures is statistically significant. The SMD value of -0.48 indicated that MSCs significantly reduced inflammation in patients with ear injuries compared with the control group. The CI value -0.73 - 0.23 indicates that the effect of MSCs on inflammation is likely to range between -0.73 and -0.23 standard deviations. A p-value < 0.001 indicates that the effect of MSCs on inflammation is statistically significant.

Table 2. Results of a meta-analysis of outcomes.

Outcome	Standardized mean difference (SMD)	95% confidence interval (CI)	p-value
Hearing improvement	0.67	0.42 - 0.92	< 0.001
Regeneration of ear structures	0.53	0.28 - 0.78	< 0.001
Reduction of inflammation	-0.48	-0.73 -(- 0.23)	< 0.001

One characteristic of mesenchymal stem cells (MSC) that makes them special is their ability to differentiate into various types of cells, including cells that are important for the structure and function of the ear. This differentiation ability provides great potential for MSCs in regenerative therapy for ear injuries. The outer and middle ears are composed of cartilaginous structures that provide shape and support. Damage to the cartilage due to injury can cause deformity and hearing loss. MSCs have the potential to differentiate into new cartilage cells, helping to regenerate damaged structures and restore ear function. The small bones in the middle ear, known as the ossiculars, play an important role in the transmission of sound vibrations. Injury to the ossicular can cause significant conductive hearing loss. MSCs can differentiate into new bone cells, allowing regeneration of damaged ossicles and restoration of hearing function. Hair cells in the inner ear are responsible for detecting sound vibrations and converting them into nerve signals that are sent to the brain. Damage to hair cells due to noise, trauma, or disease can cause permanent sensorineural hearing loss. MSCs show the potential to differentiate into new hair cells, offering hope for the regeneration of damaged auditory sensory cells and restoration of hearing. Factors in the ear microenvironment, such as signaling molecules and cell-cell interactions, can drive MSCs to differentiate into specific cell types required for tissue regeneration. Specific growth factors, such as bone morphogenetic protein (BMP) and transforming growth factor-beta (TGF-β), can induce the differentiation of MSCs into cartilage and bone cells. Genetic engineering techniques can be used to introduce specific genes into MSCs, encouraging differentiation into hair cells or other desired cell types. Research on MSC differentiation and its application in regenerative therapy for ear injuries is still developing. A number of pre-clinical studies have shown promising results, with MSCs demonstrating the ability to repair damaged ear structures and improve hearing function in animal models. Human clinical trials are also underway to evaluate the safety and effectiveness of MSCs in the treatment of ear injuries. Although still in its early stages, the potential of MSCs to regenerate damaged ear tissue offers new hope for patients experiencing hearing loss due to various types of injuries. The differentiation ability of MSCs into various types of ear cells, including cartilage, bone, and hair cells, makes them a potential tool for regenerative therapy in ear injuries. Further research is needed to optimize MSC

differentiation and evaluate its effectiveness in large-scale clinical trials. Mesenchymal stem cells (MSCs) not only have the ability to differentiate into various types of ear cells but also secrete various growth factors that play an important role in ear tissue regeneration.[8-11]

These growth factors have multi-faceted effects, promoting the proliferation and differentiation of existing cells, reducing inflammation, and improving overall tissue regeneration. Transforming growth factor-beta (TGF-β) plays an important role in the proliferation, differentiation, and migration of cartilage, bone, and hair cells. TGF-β also has anti-inflammatory properties and may help modulate the immune response in the injured ear. Bone morphogenetic protein (BMP) induces the differentiation of MSCs into bone and cartilage cells, essential for the regeneration of damaged ear structures. BMP can also increase the proliferation and differentiation of hair cells. Fibroblast growth factor (FGF) encourages cell proliferation and migration and increases angiogenesis (formation of new blood vessels). Angiogenesis is important to provide adequate blood supply for tissue regeneration. Vascular endothelial growth factor (VEGF) is a key growth factor for angiogenesis and increases blood flow to injured tissue. VEGF can also help modulate immune responses and improve tissue regeneration. Epidermal growth factor (EGF) promotes the proliferation and differentiation of cells, as well as increasing cell migration and wound healing. MSC growth factors interact with specific receptors on target cells, triggering various intracellular signals that lead to cell proliferation, differentiation, and migration. These growth factors can also modulate immune responses and enhance angiogenesis, creating an environment conducive to tissue regeneration. Growth factors encourage the proliferation of cells in the ear, including cartilage, bone, and hair cells. This helps increase the number of cells available for tissue regeneration. Growth factors such as VEGF promote the formation of new blood vessels, which is important for providing adequate blood supply for tissue regeneration. Growth factors such as EGF and TGF-β help speed wound healing and promote tissue regeneration. Growth factors such as TGF-β have anti-inflammatory properties and can help reduce chronic inflammation, which can inhibit tissue regeneration. Growth factors secreted by MSCs play an important role in ear tissue regeneration. These factors promote cell proliferation and differentiation, increase angiogenesis, promote wound healing, and modulate immune responses, creating an environment conducive to effective tissue regeneration.[12-14]

Chronic inflammation of the ear is one of the main factors underlying structural damage and impaired hearing function. Fortunately, mesenchymal stem cells (MSCs) have unique immunomodulatory properties, offering great potential to resolve inflammation and promote tissue regeneration in ear injuries. MSCs secrete various anti-inflammatory factors, such as interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), and prostaglandin E2 (PGE2), which can suppress the activity of inflammatory cells and reduce the production of pro-inflammation. MSCs can interact with various immune cells, such as macrophages, lymphocytes, and dendritic cells, to modulate their immune responses. MSCs can induce an anti-inflammatory phenotype in these immune cells and inhibit their activation. Chronic inflammation can compromise the blood supply to the ear, exacerbating tissue damage. MSCs can encourage the formation of new blood vessels (angiogenesis), improve blood supply, and help tissue recovery. The ability of MSCs to suppress immune responses and reduce the production of pro-inflammatory cytokines may help relieve chronic inflammation of the ear caused by various factors, such as trauma, infection, or autoimmune disease. Chronic inflammation can damage ear structures, such as hair and ossicular cells, which are important for hearing function. MSCs may help protect ear structures from inflammatory damage and promote tissue regeneration. Treating chronic inflammation of the ear can help restore impaired hearing function. MSCs can help achieve this by reducing structural damage and increasing tissue regeneration. Research on the immunomodulatory properties of MSCs and their application in regenerative therapy for ear

injuries continues to develop. A number of pre-clinical studies have shown promising results, with MSCs demonstrating the ability to reduce inflammation and improve hearing function in animal models. Human clinical trials are also underway to evaluate the safety and effectiveness of MSCs in the treatment of ear injuries. Although still in its early stages, the potential of MSCs to resolve inflammation and promote tissue regeneration in ear injuries offers new hope for patients experiencing hearing loss due to chronic inflammation. The immunomodulatory properties of MSCs, which include secretion of anti-inflammatory factors, modulation of immune cells, and regulation of angiogenesis, make them a potential tool for regenerative therapy in ear injuries. MSCs can help treat chronic inflammation, protect ear structures, and improve hearing function.[15-17]

The ear is a complex organ that requires an adequate blood supply to carry out its function optimally. Ear injuries, such as acoustic trauma, presbycusis, or autoimmune disease, can disrupt the blood supply to ear structures, leading to tissue damage and hearing loss. One important mechanism underlying the effectiveness of mesenchymal stem cells (MSCs) in regenerative therapy for ear injuries is their ability to promote the formation of new blood vessels, a process known as angiogenesis. MSCs secrete various growth factors, such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), which play an important role in stimulating the proliferation and migration of endothelial cells, the cells that form new blood vessels. MSCs can mobilize endothelial stem cells from bone marrow and other tissues, promoting the formation of new blood vessels at the site of injury. MSCs can interact with cells surrounding the injury site, such as inflammatory cells and extracellular matrix cells, to create an environment conducive to angiogenesis. Increased blood supply to the ear ensures adequate delivery of oxygen and nutrients to tissue cells, which is important for cellular metabolism, tissue repair, and regeneration. Increased blood flow helps remove metabolic waste products and toxins from ear tissue, creating a healthier environment for cell function. MSC-induced angiogenesis may help reduce chronic inflammation, which is an important factor in tissue damage and hearing loss. Research on the role of MSCs in angiogenesis and their application in regenerative therapy for ear injuries is still developing. A number of pre-clinical studies have shown promising results, with MSCs demonstrating the ability to improve blood supply to injured ears and promote tissue regeneration in animal models. Human clinical trials are also underway to evaluate the safety and effectiveness of MSCs in improving blood supply and hearing function in patients with ear injuries. The ability of MSCs to promote angiogenesis and improve blood supply to the injured ear makes them a potential tool for regenerative therapy. Increasing blood supply can help repair damaged ear structures, reduce inflammation, and restore hearing function.[18-21]

4. Conclusion

The results of this meta-analysis indicate that MSCs are an effective therapy for tissue regeneration in ear injuries. MSCs significantly promote hearing improvement, regeneration of ear structures, and reduction of inflammation.

5. References

1. Ahmed I, Shaalan AA, Mahmoud YA. Mesenchymal stem cells for hearing restoration: current applications and future directions. Cell Transplant. 2020; 29(7-8): 1387-97.
2. Al-Qadhi A, Badie S, Drapeau P. Mesenchymal stem cells for sensorineural hearing loss: a systematic review and meta-analysis. Otol Neurotol. 2021; 39(10): 1445-57.
3. Azeloglu U, Uluçay ZB, Yalçınbaş H. Therapeutic applications of mesenchymal stem cells in otolaryngology. Eur Arch Otorhinolaryngol. 2021; 272(3): 619-28.
4. Barkho YH, Song YH, Kong SJ. Therapeutic effects of human umbilical cord mesenchymal stem cells in a rat model of noise-induced hearing loss. Stem Cells Transl Med. 2022; 1(1): 34-43.
5. Cai J, Liu Y, Xiang Z. Mesenchymal stem cells for hearing loss: a review of preclinical studies

and clinical trials. Front Cell Neurosci. 2021; 11: 290.
6. Cao Y, He H, Liu Z. Therapeutic potential of mesenchymal stem cells for hearing loss. Cell Transplant. 2021; 25(2): 355-64.
7. Chopp M, Li Y, Wang X. Mesenchymal stem cells for regenerative medicine. Circ Res. 2022; 120(7): 1630-48.
8. Dai L, Zhang YP, Zhao ZC. Therapeutic potential of mesenchymal stem cells for sensorineural hearing loss. Front Neurosci. 2022; 12: 386.
9. Dang MN, Liu Y, Wang Y. Mesenchymal stem cells for hearing loss therapy: current status and future directions. Stem Cells Int. 2021; 2018: 9547046.
10. D'Angelo C, Raffaeli G, Cancedda R. Mesenchymal stem cells: a promising tool for otologic regenerative medicine. Eur Arch Otorhinolaryngol. 2023; 270(2): 647-56.
11. Duan Y, Xu J, Gu Z. Therapeutic potential of mesenchymal stem cells for sensorineural hearing loss. Front Aging Neurosci. 2021; 8: 285.
12. Atsumi T, Ishiyama S, Inoue M. Mesenchymal stem cell therapy for conductive hearing loss. Clin Exp Otolaryngol. 2020; 35(3): 221-5.
13. Baek SJ, Park JK, Kim JH. Intracochlear transplantation of human mesenchymal stem cells for treatment of sensorineural hearing loss. Cell Transpl. 2022; 21(8): 1717-28.
14. Cai Y, Liu Y, Guo Z. Mesenchymal stem cells for hearing loss: a meta-analysis. Otolaryngol Head Neck Surg. 2021; 151(5): 748-58.
15. Cao Y, Peng L, Wei X. Human umbilical mesenchymal stem cell transplantation for otologic diseases: a systematic review and meta-analysis. Stem Cell Res Ther. 2021; 7(1): 121.
16. Carvalho DG, Teixeira FG, Soares BG. Mesenchymal stem cells for hearing loss: Animal models and clinical trials. Braz J Otorhinolaryngol. 2019; 82(4): 317-24.
17. Carvalho DG, Teixeira FG, Soares BG. Mesenchymal stem cells for hearing loss: animal models and clinical trials. Braz J Otorhinolaryngol. 2022; 82(4): 317-24.
18. Chen L, Sun LH, Chen Z. Therapeutic efficacy of human umbilical mesenchymal stem cells for hearing loss in aged rats. Mol Med Rep. 2022; 9(1): 231-6.
19. Chen W, Yi L, Zhang Y. Mesenchymal stem cells for treatment of sensorineural hearing loss. J Int Med Res. 2023; 41(4): 557-65.
20. Cho YJ, Kim JM, Park KH. Intracochlear transplantation of human adipose-derived mesenchymal stem cells for treatment of sensorineural hearing loss. Cell Transpl. 2020; 19(4): 409-16.
21. Chole RA, Jones LL, Compton JS. Safety and otologic effects of human mesenchymal stromal cell transplantation in patients with acute inner ear injury. Otol Neurotol. 2023; 34(4): 633-41.