

Original Article

Effects of Insulin-Like Growth Factor (IGF-1) in Patients with Sensorineural Hearing Loss

Varun Jitendra Dave, Anagha Joshi, Renuka Bradoo, Manish Prajapati, Kshitij Shah

Lokmanya Tilak Municipal Medical College, Sion Hospital, Mumbai, India

Cite this article as: Dave V, Joshi A, Bradoo R, Prajapati M, Shah K. Effects of insulin-like growth factor (IGF-1) in patients with sensorineural hearing loss. *J Int Adv Otol*. 2021;17(3):207-214.

OBJECTIVES: (1) To test the effect of local administration of insulin-like growth factor-1 (IGF-1) in patients with sensorineural hearing loss (SNHL). (2) To test the effect of local administration of IGF-1 in patients with ototoxicity.

METHODS: Forty patients with SNHL were included in the study. Their hearing thresholds at different frequencies (0.5, 1, 2, and 4 kHz) along with the average hearing threshold were noted. The patients were then randomly allocated to 2 groups and were treated with IGF-1 via one of the following routes: (1) intratympanic injection and (2) Gelfoam.

Patients were followed-up at weekly intervals for 6 weeks but follow-up PTA was done at 3 weeks, 6 weeks, and 6 months only.

RESULTS: Forty patients (25 male, 15 female) participated in the study. Their age ranged from 13 to 63 years, with a mean of 31.3 years. Nineteen (47.5%) patients exhibited some degree of recovery after 6 months of follow-up, while 21 (52.5%) did not exhibit any recovery. Fourteen (35%) patients showed slight recovery (SR), 1 (4%) patient showed marked recovery, and complete recovery was observed in 4 (10%) patients. Twelve of the 20 patients who underwent treatment using Gelfoam showed improvement in hearing (measured as a reduction in hearing threshold), while only 7 of the 20 patients who underwent intratympanic injection showed such improvement. Among adverse reactions, the most common was pain (88%) which typically did not last beyond 3 days. Other adverse reactions observed were dizziness (24%) and headache (20%). One patient suffered from acute suppurative otitis media (ASOM) and had a perforation in the tympanic membrane. However, this was treated successfully with medications.

CONCLUSION: Intratympanic IGF-1 is a novel drug that has shown early promise in controlling and reversing SNHL.

KEYWORDS: IGF-1, SNHL, Gelfoam, intratympanic injection

INTRODUCTION AND BACKGROUND

Hearing loss is the most common sensory deficit affecting human beings. While conductive hearing loss (CHL) can be reversed, sensorineural hearing loss (SNHL) is largely irreversible. Although sudden sensory hearing loss (SSHL) is routinely treated by systemic corticosteroids, only 20% of all patients respond to the treatment. SNHL, due to other causes such as presbycusis, ototoxicity, and autoimmune disorders, does not respond to any medical therapy, and the most common treatment options offered are hearing aids or cochlear implants. These are expensive, require maintenance, and have low cosmetic appeal. Thus, there is a need for a therapy that can effectively stop or reverse the degenerative process leading to hearing loss. Since the turn of the century, regenerative therapy has acquired a prominent role in disciplines such as orthopedics, rheumatology, and sports medicine. However, it has failed to have any significant impact on the treatment of hearing disorders. Due to this, hearing aids and cochlear implants remain the only viable option for the management of SNHL. This can be attributed to 2 main reasons. First, that mammalian cochlear hair cells (HCs) inherently lack the ability to repair or regenerate themselves.¹ The second reason is that researchers have not been able to devise a definite route of administration that ensures a constant delivery of drugs or viral vectors to the inner ear.² These 2 factors combined have rendered all efforts to regenerate human cochlear HCs futile. More insight into the action of growth factors, along with recent advances in the field of gene therapy, has made it possible to induce transdifferentiation of supporting cells (SC) into HCs and prevent apoptosis of HCs when exposed to toxic stimuli.³

Insulin-Like Growth Factor-1

IGF-1 is the anabolic effector hormone of the growth hormone-releasing hormone–somatomedin–growth hormone axis. Secreted by the liver, it is an endocrine polypeptide hormone comprising 70 amino acids, with a molecular weight of 7649 daltons and a half-life of 8–16 hours. It is referred to as “insulin-like” because of its structural similarity to proinsulin, although functionally, it has very minimal insulin-like actions.⁴

The IGF System

The IGF system consists of IGF-1 and IGF-2, IGF binding proteins (IGFBPs), and IGF receptors. IGF-1 and IGF-2 are members of a large family of insulin-related peptides, which also include proinsulin, insulin, and relaxin. The gene that encodes for pre-pro-IGF-1, an inactive precursor, is located on chromosome 12, while the gene that encodes IGF-2 is located on chromosome 11. There is a 62% sequence homology between the 2. However, the potency of IGF-1 is greater than that of IGF-2, and so only IGF-1 will be considered here. There are 6 IGFBPs and almost all the IGF-1 is found bound to these proteins. IGFBP-3 is the most important of them, as the majority of IGF-1 is attached to it, along with a component known as the acid-labile subunit. IGFBPs regulate the free availability of IGF-1 and its biological functions. The IGF-1 receptor is a tyrosine-kinase receptor that resembles the insulin receptor. It is made up of 2 α and 2 β chains that are formed from a single polypeptide chain, and are connected by a disulfide bond.⁴

Aims and Objectives of the Study

1. To test the effect of local administration of IGF-1 on patients with SNHL.
2. To test the effect of local administration of IGF-1 on patients with ototoxicity.

METHODS

The study was a single-center case series, conducted from January 2018 to January 2019. The observation period for each patient was 6 months and the total sample size was 40.

Patients with SNHL were identified by clinical examination, otoscopy, tuning fork tests, and pure-tone audiogram. These patients underwent MRI, brainstem evoked response audiometry (BERA), tone decay test (TDT), and short increment sensitivity index (SISI) to determine if hearing loss was due to cochlear or retrocochlear causes.

Inclusion Criteria

1. Patients with acute or chronic sensory hearing loss.
2. Patients suffering from hearing loss as a result of ototoxicity.
3. Patients who gave consent for the study.

Exclusion Criteria

1. Patients with CHL.
2. Patients with mixed hearing loss.
3. Patients with SNHL due to space-occupying retrocochlear pathologies such as vestibular schwannoma and meningioma.

The audiometer used in our study had a hearing range from –10 to 110 dB HL in 5 dB steps. The tone stimulus was pure-tone and frequency range was 125 to 8000 Hz.

Accuracy of the audiometer:

- a) Frequencies: better than $\pm 3\%$
- b) Hearing Level: within ± 3 dB of indicated level from 125 to 5000 Hz and ± 5 dB at 6000 Hz and higher.

Total harmonic distortion was $< 2\%$ and calibration was IEC 645, ANSI S3.6. The standards were Type 4 audiometer and EN 60645-1 for audiometers.

Audiology Room Design

The setup was a 2-room air-conditioned setup with double-walled sound-attenuating doors and windows, with each room measuring about 12 m² in area. The ambient noise in the room was 0 to 10 dB with a reverberation time of less than 0.25 seconds.

As some of the patients who participated in the study were above 50 years of age, it was presumed that there could be a more subtle reduction in processing efficiency that stems from synaptic dysfunction and degeneration of cochlear nerve axons. This type of cochlear dysfunction has sometimes been referred to as “hidden hearing loss,” because it is not detectable using standard pure-tone audiometry or MRI. Among other factors, hidden hearing loss has been linked to difficulty in encoding near-threshold sounds, auditory attention, and possibility of loss of neurons of the auditory (CN VIII) nerve due to natural aging, which could not be detected on the MRI.⁵ Thus, to rule out the same, the following tests were done:

SISI (Short Increment Sensitivity Index)

Patients with cochlear lesions can distinguish smaller changes in intensity of pure tone better than people with normal hearing, and are also better than individuals with conductive or retrocochlear pathology. The SISI test is used to differentiate a cochlear lesion from a retrocochlear lesion.

Tone Decay Test (TDT)

This test is a measure of nerve fatigue and is used to detect retrocochlear lesions. An individual with normal hearing can hear a tone continuously for 60 seconds. When there is nerve fatigue, the patient stops hearing a tone earlier than this time period.

Brainstem Evoked Response Audiometry (BERA)

BERA is also called BAER or BAEP (brainstem auditory evoked response or potential) and is used to elicit brainstem responses to auditory stimulation by clicks or tone bursts. It is a non-invasive technique to examine the integrity of central auditory pathways through the CN VIII, pons, and midbrain. Patients with retrocochlear SNHL were excluded from the study. Patients who had SNHL for less than 2 months and more than 1 year were also excluded. Forty patients with SNHL were included in the study. Their hearing thresholds at different frequencies (0.5 kHz, 1, 2, and 4 kHz), along with the average hearing threshold were noted.

The patients were then randomly allocated to 2 groups, namely, intratympanic injection and Gelfoam, according to the mode of IGF-1 administration.

Table 1. Criteria for Hearing Improvement Determined by the Sudden Deafness Research Committee of the Japanese Ministry of Health, Labour and Welfare in 1984

Improvement	Criteria
Complete recovery	Recovery of a hearing level within 20 dB at all 5 frequencies tested (0.25, 0.5, 1, 2, and 4 kHz) or recovery to the same level as the opposite side in pure-tone audiometry
Marked recovery	More than 30 dB recovery in the mean hearing level at the 5 frequencies tested
Slight recovery	Recovery of 10-29 dB in the mean hearing level at the 5 frequencies tested
No recovery	Recovery less than 10 dB in the mean hearing level at the 5 frequencies tested

Method of Randomization

Patients were asked to select a number between 1 and 40, and that number was assigned to the patient. Patients who chose an odd number (e.g., 1, 3, 5, and so on) were assigned to the intratympanic injection group, and those who chose an even number (e.g., 2, 4, 6, and so on) were assigned to the Gelfoam group.

Intratympanic Injection

The tympanic membrane was anesthetized using 10% lignocaine spray. Using a 27-gauge needle, a small air vent was made in the anterosuperior quadrant of the ear drum to remove air from the middle ear. Next, 0.5ml IGF-1 was injected in the middle ear space through a separate perforation made in the same quadrant.

Site of Injection

There is no consensus as to which quadrant is the best for intratympanic injections, but there are many studies that report injection into the anterosuperior quadrant. Moreover, it is postulated that the amount of drug that reaches the inner ear is directly proportional to the time that the drug is present in the middle ear. Thus, the drug was not injected through the posteroinferior quadrant, which is directly adjacent to the round window, as much of the drug would leak through the air vent back into the external ear.^{6,7,8}

Gelfoam

The ear canal was anesthetized using 2% lignocaine with adrenaline. The tympanomeatal (TM) flap was elevated and Gelfoam soaked with IGF-1 was placed in the round window niche. The ear canal was packed after repositioning the TM flap. Both procedures were carried out under day care. Patients were followed-up at weekly intervals for 6 weeks; however, follow-up PTA was done at 3 weeks, 6 weeks, and 6 months. Each patient's subjective improvement in hearing and tinnitus was noted as well. The following outcomes were noted:

1. Change in hearing threshold in 0.5, 1, 2, and 4 kHz frequencies
2. Subjective change in hearing acuity
3. Change in tinnitus
4. Adverse effects such as
 - i. Pain
 - ii. Vertigo
 - iii. Further hearing loss
 - iv. Otitis media

Based on their recovery, patients were classified into 1 of 4 categories for hearing improvement, according to criteria determined by the Sudden Deafness Research Committee of the Japanese Ministry

of Health, Labour and Welfare in 1984. These categories and the corresponding criteria are shown in Table 1.

Criteria for Improvement⁹

Statistics Data were entered in an MS Excel spreadsheet and analyzed with the help of MS Excel and SPSS V20 (available freely). Qualitative data were expressed with frequencies and percentages.

RESULTS

Of the 40 patients in the sample, 25 were males and 15 were females. The mean age was 31.3 years (13-63 years). Patients who had bilateral hearing loss were considered as 2 individual patients, as both the ears were treated and hence considered separately. Table 2 shows the different causes of SNHL in our study. All patients with ototoxicity were affected by tuberculosis. All of them had undergone treatment with kanamycin. We found that 72% of the patients had associated symptoms, the most common of which was tinnitus. Other associated symptoms were dizziness, headache, and difficulty in sound localization. These symptoms were more common in patients with ototoxicity. The average time between onset of hearing loss and intervention was 63 days (2 days-5 years). Patients who were within the 30-day period of diagnosis of SNHL were first treated with systemic and local steroids, as it would be unethical to not offer them steroids for the sake of the study. Seven days after the completion of the steroid regimen, PTA was repeated. This PTA was considered baseline, after which IGF-1 therapy was initiated.

Hearing

As shown in Table 4, 21 (52.5%) out of 40 patients did not exhibit any change in their hearing, while 14 (35%) patients showed slight recovery, 1 (4%) patient showed marked recovery, and 4 (10%) patients demonstrated complete recovery. Twelve of the 20 patients who underwent treatment using Gelfoam showed improvement in hearing while only 7 of the 20 patients who were administered intratympanic injection showed a reduction in hearing threshold.

As is evident from Table 5, the chances of recovery significantly decreased as the duration of hearing loss increased.

Table 2. Causes OF SNHL Within the Sample

Etiology	Number of Patients
Ototoxicity	15
Spontaneous SNHL	24
Presbycusis	1

SNHL, sensorineural hearing loss.

Table 3. Management Profile of all 40 Patients

Patient	Age/Sex	Cause of SNHL	Duration of disease	Injected (I) vs. Gelfoam (G)	Pre-treatment hearing threshold	3 weeks	6 weeks	6 months	Recovery
1	38/M	Ototoxicity	11 months	I	105	105	104	104	NR
2	38/M	Ototoxicity	11 months	I	109	100	100	100	NR
3	19/M	SSHL	5 months	G	98	85	80	80	SR
4	22/F	SSHL	7 months	I	62	46	40	40	SR
5	22/F	SSHL	7 months	I	56	40	34	34	SR
6	26/F	Ototoxicity	8 months	G	45	25	20	15	CR
7	21/F	Ototoxicity	10 months	I	65	65	65	65	NR
8	22/F	SSHL	6 months	G	70	55	45	40	MR
9	18/M	SSHL	4 months	I	105	95	90	85	SR
10	13/M	SSHL	11 months	G	64	55	50	50	SR
11	19/M	SSHL	11 months 20 days	G	40	25	25	20	CR
12	22/F	SSHL	3 months	I	100	80	80	75	SR
13	56/M	Ototoxicity	6 months	G	76	65	60	60	SR
14	56/M	Ototoxicity	6 months	G	80	80	80	80	NR
15	19/F	SSHL	2 months	G	95	85	80	80	SR
16	28/M	SSHL	6 months	I	55	55	55	55	NR
17	28/M	SSHL	6 months	I	50	50	50	50	NR
18	19/F	SSHL	10 months	G	45	40	38	38	NR
19	26/M	Ototoxicity	10 months	G	60	55	55	55	NR
20	26/M	Ototoxicity	10 months	G	60	60	60	60	NR
21	21/F	SSHL	8 months	I	55	45	45	45	NR
22	54/F	SSHL	4 months	I	60	40	40	40	SR
23	32/M	SSHL	11 months	I	54	54	54	54	NR
24	18/F	Ototoxicity	2 months 10 days	G	46	30	30	25	SR
25	60/F	SSHL	9 months	G	50	45	45	45	NR
26	33/M	SSHL	11 months	I	60	55	55	55	NR
27	34/F	SSHL	11 months	G	110	110	110	110	NR
28	48/M	Ototoxicity	2 months	G	60	40	40	40	SR
29	21/M	SSHL	2 months 15 days	G	100	90	85	85	SR
30	22/M	Ototoxicity	8 months	I	35	20	20	20	CR
31	22/M	Ototoxicity	8 months	I	35	20	20	20	CR
32	21/M	Ototoxicity	3 months	I	70	70	70	70	NR
33	61/M	Presbycusis	7 months	G	66	66	66	60	NR
34	41/M	SSHL	5 months	I	40	30	25	25	SR
35	42/M	SSHL	7 months	G	60	60	60	60	NR
36	44/M	Ototoxicity	3 months	G	75	75	75	75	NR
37	39/M	SSHL	10 months	I	46	40	36	36	NR
38	39/M	SSHL	3 months	I	46	46	46	46	NR
39	41/F	SSHL	11 months	G	80	70	65	65	SR
40	24/F	Ototoxicity	6 months	I	70	65	65	60	NR

SNHL, sensorineural hearing loss; CR, complete recovery; MR, marked recovery; NR, no recovery; SR, slight recovery; SSHL, spontaneous sensorineural hearing loss.

Table 4. Recovery Pattern of the Patients

Recovery Pattern	Number of Patients
No recovery (NR)	21
Slight recovery (SR)	14
Marked recovery (MR)	1
Complete recovery (CR)	4

Table 5. Recovery Pattern According to Duration of Hearing Loss

Duration of Hearing Loss	Recovery		Total
	Yes	No	
2-3 months	5	3	8
3-6 months	6	4	10
6-9 months	5	4	9
9-12 months	3	10	13

As shown in the above graph (Figure 1), IGF-1 treatment was more successful in patients with SSHL than in patients with ototoxicity. Fourteen out of 24 (59%) patients with SSHL showed some form of recovery while only 6 out of 15 (40%) patients with ototoxicity showed hearing improvement.

Controls

The results of the study were compared with historical controls to test the efficacy of IGF-1 with other treatment modalities such as steroids (local and systemic), antiviral agents, hemodilution agents, minerals, vitamins (methylcobalamin and vitamin E), and hyperbaric oxygen (HBO2).³⁻⁵ It was found that while some of these drugs (steroids and vitamin E) were effective in reversing sudden SNHL, none of them were effective in chronic SNHL.

Adverse Reactions

The most common adverse reaction was pain (88%); however, this typically did not last beyond 3 days. Other adverse reactions observed were dizziness (24%) and headache (20%). One patient suffered from ASOM and had a perforation in the tympanic membrane. However, it was successfully treated with medications. None of the adverse reactions were permanent. None of the patients had a further increase in hearing loss after the treatment.

DISCUSSION

Why IGF-1?

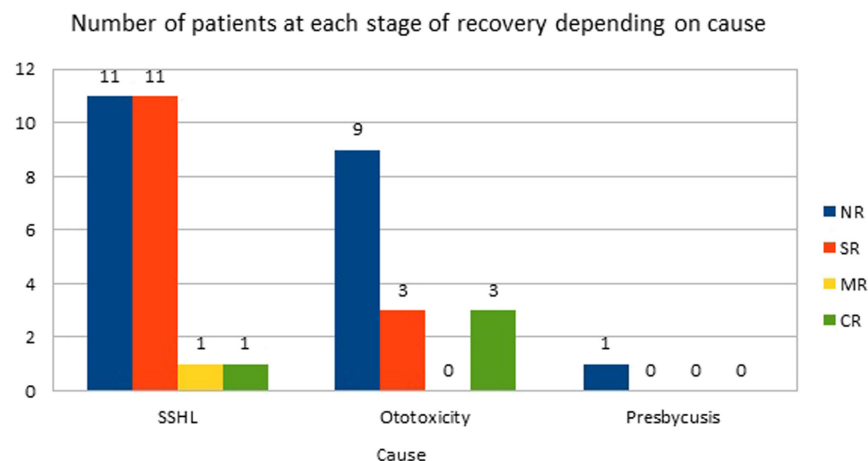
During the late 20th century, Represa¹⁰ and Neito¹¹ found that insulin had a mitogenic effect on inner ear HCs. However, the doses required for this were significantly greater than those required to completely saturate the insulin receptor.¹² This led to the hypothesis that the effects of insulin could be mediated via a low-affinity, structurally similar receptor. This hypothesis was confirmed in 1995 by Leon et al.,¹¹ when they demonstrated the up-regulatory effects of IGF-1 on otic vesicles and cochleovestibular ganglion of chicken otocyst. They showed that after being treated with IGF-1, the otic vesicles moved through different stages of maturation at a faster rate than they would have otherwise. Since then, numerous studies have not only confirmed this but have also laid down the mechanism and downstream signaling pathways that are involved in effecting IGF-1 actions.

The first pathway is the phosphatidylinositol 3-kinase (PI3K)/Akt pathway in which phosphorylated PI3K activates Akt. The second pathway, the MEK/ERK pathway, is composed of Ras, Raf, and mitogen-activated protein kinase (MAP2K or MEK), and activates the mitogen-activated protein kinases or extracellular signal-regulated kinases (ERK) 1/2.

The downstream effects of the 2 pathways include cell survival, cell cycle promotion, and anti-apoptotic response with cell proliferation respectively. PI3K also activates the MEK/ERK pathway through protein kinase C (PKC).^{2, 13}

The PI3K/Akt pathway maintains the number of inner hair cells (IHCs) through the inhibition of apoptosis. When activated in the Hensen's and Claudius' cells, the MEK/ERK pathway induces cell cycle promotion in these cells which partly contributes to the maintenance of the outer HCs (OHCs). In contrast to this, dexamethasone, which is frequently administered for the treatment of sudden SHL, activates only the PI3K pathway.

Over the past 20 years, many in vitro studies and explant cultures have demonstrated the protective and proliferative effect of IGF-1 on mammalian cochlea. Rubel et al. conducted a study in quail explants

**Figure 1.** Recovery pattern in relation with the cause of SNHL.

to show that IHCs, in fact, do have regenerative potential.¹⁴ After Leon et al. observed that IGF-I is a potent growth factor in the otic vesicle and that the CVG and IGF-I high-affinity binding sites are present in the otic vesicle and in the CVG during proliferative stages, numerous other researches have also confirmed the same.¹¹ In 1997, Oesterle et al. showed that when chicken explants were treated with different growth factors, IGF-1 and insulin caused DNA proliferation of sensory epithelia whereas other growth factors such as EGF, bombesin, and TGF- α had no effect.¹⁴ Similar results were observed by Zheng et al. in rat epithelia.¹⁵ Okano et al.¹⁶ showed that IGF-1 is essential in the development of mouse cochlea and also regulates the timing of sensory cell differentiation. In 2007, Park et al.¹⁷ studied the actions of IGF-1, IGFBP-4, and IGFBP-5 in neomycin-treated mouse cochlea and found that IGF-I, IGFBP-4, and -5 alone and IGF-I+IGFBP-5 mixture stimulated hair cell survival and prevented neomycin-induced hair cell loss in the sensory epithelial culture of mouse utricles. In human beings, SNHL occurs in patients with mutations in the *Igf1* gene, primary IGF-1 deficiency, or low serum IGF-1 levels due to other genetic defects, indicating the importance of IGF-1 in hearing.

This prompted the first human trial conducted by Ito et al.¹⁸ in 2010, in which they tested the efficacy of IGF-1 in glucocorticoid-resistant sudden SNHL. They used gelatin hydrogel as a delivery device for the transfer of IGF-1 in the inner ear. It has been shown that IGF-1 is found in the perilymph 3 days after being administered in the middle ear using gelatin hydrogel. They used historical controls in which HBO2 was used to treat SNHL. They showed that at 24 weeks, 56% of patients (14/25) showed recovery from SNHL, who were otherwise resistant to any other form of treatment. No serious adverse effects were noted.

In 2014, a randomized controlled trial was conducted at the same hospital, to compare the efficacy of IGF-1 with intratympanic dexamethasone. They found that in the IGF-1 group, 66.7% (95% CI, 52.9–78.6%) of the patients showed hearing improvement compared to 53.6% (95% CI, 39.7–67.0%) of the patients in the Dex group. A trend, however, was observed: there was a higher proportion of patients with 30 dB HL improvements in pure-tone average hearing thresholds in the IGF-1 group than in the intratympanic steroids group. The difference in changes in pure-tone average hearing thresholds over time between the 2 treatment groups was found to be statistically significant. It was concluded that IGF-1 was superior to steroids in treating SNHL. We did not find any other studies conducted in humans.¹⁹

Hatano et al.²⁰ performed a study where they administered antioxidants vitamin E and C as adjuvants to steroids and found that the hearing gain after therapy was 29.4 dB and the improvement rate was 63.3% in the study group, compared with 18.5 dB and 44.0% in the control group. Significant improvement was seen in the hearing gain and recovery rate in the study group.

Racic et al.²¹ tested the effects of HBO2 therapy on 17 patients and found that the average hearing level for all patients and for all 5 basic frequencies was 67.8 dB before therapy, in comparison with 21.6 dB after oxygen therapy ($P = .0003$). However, there is a need for prospective, random, double-blind studies of the effects of HBO2 therapy on SSHL, on a large number of patients.

Stokroos et al.²² conducted a similar study to test the benefits of acyclovir, an antiviral agent, in 44 patients with idiopathic sudden SNHL and found that no beneficial effect of combining acyclovir with prednisolone could be established in ISSHL.

Similarly, there was no difference in audiometric outcomes reported across all other studies of antiviral and hemodilution agents.²³ The recent discovery of stem cells in the adult inner ear, that are capable of differentiating into HCs, as well as the finding that embryonic stem cells can be converted into HCs, raise hope for the future development of stem-cell-based treatment regimens.²⁴ It is now known that not only is IGF-1 essential for the development of the inner ear in the fetal stage but that it can also maintain the HC number in the postnatal stage when exposed to various kinds of insults. Ito et al. examined the effect of IGF-1 on neomycin-treated mouse cochlea explant.²⁵ It has also been shown that the SCs take part in the regeneration of HCs through transdifferentiation and proliferation. Nakagawa et al. demonstrated that regeneration of avian HCs is based on both proliferation and transdifferentiation of SCs that surround HCs. Thus, SCs are a source of HC regeneration.^{11,26} Different studies conducted in gerbils and adult rats illustrate a similar effect on postnatal mammalian cochlear HCs after exposure to ischemia and noise, respectively.²⁵

IGF-1 Deficiency

The importance of IGF-1 in mammalian hearing can be further ascertained by the fact that patients with IGF-1 deficiency invariably suffer from SNHL. Patients of Laron syndrome, a rare congenital disorder characterized by the deficiency of IGF-1, are affected by varying degrees of SNHL. Furthermore, Laron et al. proved that supplementing these patients with daily subcutaneous recombinant IGF-1 improves hearing across all frequencies.^{27, 28, 29, 30, 31}

Drug Delivery Systems³²

With the development of novel techniques in tissue engineering and tissue regeneration, it becomes imperative that a route of drug administration be developed to ensure the delivery of a stable and measurable amount of drug to the inner ear. However, the inner ear remains an elusive organ as it is still largely inaccessible by present-day drug delivery systems.

Blood–Labyrinth Barrier (BLB)

The blood–labyrinth barrier, like the blood–brain barrier, is made up of capillary endothelial cells and tight junctions and separates the inner ear from the systemic circulation. It is located in the stria vascularis, and with a few exceptions (steroids, aminoglycosides), prevents entry of drugs into the perilymph. Moreover, blood flow to the inner ears is only 1/10 000 to 1/1 000 000th of the systemic flow. This makes systemic administration an ineffective tool in treating inner ear disorders. When administered systemically, IGF-1 is not well tolerated. It may lead to hypoglycemic episodes, fluid retention, palpitations, headache, and joint pain. Many *in vitro* studies have shown that due to its mitogenic action, it may contribute to the growth of tumors such as breast and colorectal cancer and may also cause resistance to chemotherapy.³³

Intratympanic Delivery

Intratympanic delivery is currently the most widely used method in clinical practice. The drug is administered in the middle ear space, and then traverses through the round window membrane (RWM) into the

scala tympani. Different approaches include direct delivery by a canula, Silverstein MicroWick, round window microcatheter, sustained-release systems (most commonly Gelfoam), and nanoparticles.

Although it is safe, only a very small amount of the drug actually reaches the inner ear. Plonket et al.¹ found that after intratympanic administration of gentamycin, only 2.5% of the administered dose reaches the basal turn of the cochlea. The interplay of various factors prevents drugs reaching the inner ear; namely the RWM acting as a physical hindrance to the entry of drugs, loss of drug through the eustachian tube, and temporal bone spaces and elimination of the drug by the middle ear mucosa. Moreover, much of the drug that reaches the scala tympani is rapidly cleared by the cochlea. This creates a gradient between the apical and basal regions of the cochlea.

Intralabyrinthine Delivery

Although this route ensures a greater amount of drug delivered to the inner ear, none of the approaches have at present been approved for use in human subjects.

Intratympanic Injection Versus Gelfoam

Both the approaches that were tried in our study had their advantages and disadvantages. The Gelfoam method had a slightly better success rate, which may be because of the greater contact time IGF-1 has with the RWM. However, it is more invasive, cannot be done as an outdoor procedure, lacks repeatability, requires some surgical expertise, and has greater potential side effects. On the other hand, intratympanic IGF-1 can be administered multiple times if needed, is done as an outpatient procedure, and has no side effects. However, it affords minimal contact time with the RWM and only approximately 2% of the drug reaches the cochlea, which may be responsible for its decreased therapeutic efficacy.¹

Future Research

During the last 30 years, it became possible to regenerate cochlear HCs, albeit in animal models. The use of growth factors (especially IGF-1), gene therapy, and stem cell transplants have shown promise in controlling as well as reversing SNHL. To the best of our knowledge, in 2010, Ito et al. conducted the first study in human subjects, in which they used intratympanic IGF-1 to successfully reverse sudden refractory SNHL. This is the second study that confirms the therapeutic effect of IGF-1 on SNHL. However, a great deal of knowledge regarding its pharmacokinetics, dosage, and potential long-term side effects still remains to be elucidated.

For all future regenerative therapies to succeed, developing a drug administration technique that ensures delivery of a high and constant dose of drug/gene vectors/stem cells to the inner ear will be vital. Substantial future research needs to be directed toward this.

Limitations

1. As the study did not use controls, it cannot be said with certainty that IGF-1 is a novel drug that can be used to reverse or cure SNHL.
2. A randomized control trial with a greater sample size and triple blinding is required to affirm the efficacy of IGF-1 in treating SNHL.

CONCLUSION

Intratympanic IGF-1 is a novel technique that continues to show promise in controlling and reversing SNHL.

Ethics Committee Approval: Ethics committee approval was obtained for the study from the hospital (Case Number IEC/907/18).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – V.D.; Design – V.D.; Data Collection and/or Processing – V.D., M.P., K.S.; Writing – V.D.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Iwai K, Nakagawa T, Endo T et al. Cochlear protection by local insulin-like growth factor-1 application using biodegradable hydrogel. *Laryngoscope*. 2006;116(4):529-533. [\[CrossRef\]](#)
2. Salt AN, Plontke SK. Principles of local drug delivery to the inner ear. *Audiol Neurotol*. 2009;14(6):350-360. [\[CrossRef\]](#)
3. Jadali A, Kwan KY. Activation of PI3K signaling prevents aminoglycoside-induced hair cell death in the murine cochlea. *Biol Open*. 2016;5(6):698-708. [\[CrossRef\]](#)
4. Laron Z. Somatomedin-1 (recombinant insulin-like growth factor-1): Clinical pharmacology and potential treatment of endocrine and metabolic disorders. *BioDrugs*. 1999;11(1):55-70. [\[CrossRef\]](#)
5. Pengse P, Delaney E, Gamper H et al. Ya-Ming Hou The neural consequences of age-related hearing loss. *Physiol Behav*. 2017;176(12):139-148.
6. Bear ZW, Mikulec AA. Intratympanic steroid therapy for treatment of idiopathic sudden sensorineural hearing loss. *Mo Med*. 2014;111(4):352-356.
7. Liu YC, Chi FH, Yang TH, Liu TC. Assessment of complications due to intratympanic injections. *World J Otorhinolaryngol Head Neck Surg*. 2016;2(1):13-16. [\[CrossRef\]](#)
8. Kosyakov S, Atanesyan A, Gunenkov A, Ashkhatunyan E, Kurlova A. Intratympanic steroids for sudden sensorineural hearing loss. *J Int Adv Otol*. 2011;7(3):323-332.
9. Byl FMJ. Sudden hearing loss: eight years' experience and suggested prognostic table. *Laryngoscope*. 1984 May;94(5 Pt 1):647-661. [\[CrossRef\]](#)
10. Represa JJ, Miner C, Barbosa E, Giraldez F. Bombesin and other growth factors activate cell proliferation in chick embryonic vesicles in culture. *Development*. 1988;103(1):87-96. [\[CrossRef\]](#)
11. León Y, Vazquez E, Sanz C et al. Insulin-like growth factor-I regulates cell proliferation in the developing inner ear, activating glycosyl-phosphatidylinositol hydrolysis and Fos expression. *Endocrinology*. 1995;136(8):3494-3503. [\[CrossRef\]](#)
12. Blakesley VA, Scrimgeour A, Esposito D, Roith D Le. Signaling via the insulin-like growth factor-I receptor : does it differ from insulin receptor signaling ? *Cytokine Growth Factor Rev*. 1996;7(2):153-159. [\[CrossRef\]](#)
13. Hayashi Y, Yamamoto N, Nakagawa T, Ito J. Insulin-like growth factor 1 inhibits hair cell apoptosis and promotes the cell cycle of supporting cells by activating different downstream cascades after pharmacological hair cell injury in neonatal mice. *Mol Cell Neurosci*. 2013;56:29-38. [\[CrossRef\]](#)

14. Oesterle EC, Tsue TT, Rubel EW. Induction of cell proliferation in avian inner ear sensory epithelia by insulin-like growth factor-I and insulin. *J Comp Neurol*. 1997;380(2):262-274. [\[CrossRef\]](#)
15. Zheng JL, Helbig C, Gao WQ. Induction of cell proliferation by fibroblast and insulin-like growth factors in pure rat inner ear epithelial cell cultures. *J Neurosci*. 1997;17(1):216-226. [\[CrossRef\]](#)
16. Okano T, Xuan S, Kelley MW. Insulin-like growth factor signaling regulates the timing of sensory cell differentiation in the mouse cochlea. *J Neurosci*. 2011;31(49):18104-18118. [\[CrossRef\]](#)
17. Park JY, Park YH, Shin DH, Oh SH. Insulin-like growth factor binding protein (IGFBP)-mediated hair cell survival on the mouse utricle exposed to neomycin: the roles of IGFBP-4 and IGFBP-5. *Acta Otolaryngol Suppl*. 2007;127(558)(suppl 558):22-29. [\[CrossRef\]](#)
18. Nakagawa T, Sakamoto T, Hiraumi H et al. Topical insulin-like growth factor 1 treatment using gelatin hydrogels for glucocorticoid-resistant sudden sensorineural hearing loss: A prospective clinical trial. *BMC Med*. 2010;8(1):76. [\[CrossRef\]](#)
19. Yamahara K, Yamamoto N, Nakagawa T, Ito J. Insulin-like growth factor 1: A novel treatment for the protection or regeneration of cochlear hair cells. *Hear Res*. 2015;330(A):2-9. [\[CrossRef\]](#)
20. Hatano M, Uramoto N, Okabe Y, Furukawa M, Ito M. Vitamin E and vitamin C in the treatment of idiopathic sudden sensorineural hearing loss. *Acta Otolaryngol*. 2008;128(2):116-121. [\[CrossRef\]](#)
21. Racić G, Petri NM, Andrić D. Hyperbaric oxygen as a method of therapy of sudden sensorineural hearing loss. *Int Marit Health*. 2001;52(1-4):74-84.
22. Stokroos RJ, Albers FWJ, Tenvergert EM. Antiviral treatment of idiopathic sudden sensorineural hearing loss : A prospective , randomized , double-blind clinical trial. *Acta Otolaryngol*. 1998;118(4):488-495. [\[CrossRef\]](#)
23. Conlin AE, Parnes LS. Treatment of sudden sensorineural hearing loss: I. A systematic review. *Arch Otolaryngol Head Neck Surg*. 2007;133(6):573-581. [\[CrossRef\]](#)
24. Li H, Corrales CE, Edge A, Heller S. Stem cells as therapy for hearing loss. *Trends Mol Med*. 2004;10(7):309-315. [\[CrossRef\]](#)
25. Fujiwara T, Hato N, Nakagawa T et al. Insulin-like growth factor 1 treatment via hydrogels rescues cochlear hair cells from ischemic injury. *NeuroReport*. 2008;19(16):1585-1588. [\[CrossRef\]](#)
26. Adler HJ, Raphael Y. New hair cells arise from supporting cell conversion in the acoustically damaged chick inner ear. *Neurosci Lett*. 1996;205(1):17-20. [\[CrossRef\]](#)
27. Attias J, Zarchi O, Nageris BI, Laron Z. Cochlear hearing loss in patients with Laron syndrome. *Eur Arch Otorhinolaryngol*. 2012;269(2):461-466. [\[CrossRef\]](#)
28. Woods KA, Camacho-Hübner C, Savage MO, Clark AJ. Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor I gene. *N Engl J Med*. 1996;335(18):1363-1367. [\[CrossRef\]](#)
29. Bonapace G, Concolino D, Formicola S, Strisciuglio PA. A novel mutation in a patient with insulin-like growth factor 1 (IGF1) deficiency. *J Med Genet*. 2003;40(12):913-917. [\[CrossRef\]](#)
30. Walenkamp MJE, Karperien M, Van D. J, Forbes BE. Homozygous and heterozygous expression of a novel IGF-I mutation. *J Clin Endocrinol Metab*. 2005; 90(5):2855-2864. (doi: [\[CrossRef\]](#))
31. Camarero G, Avendano C, Fernandez-Moreno C et al. Delayed inner ear maturation and neuronal loss in postnatal Igf-1 -deficient mice. *J Neurosci*. 2001;21(19):7630-7641. [\[CrossRef\]](#)
32. Liu H, Hao J, Li KS. Current strategies for drug delivery to the inner ear. *Acta Pharmaceutica Sinica B*. 2013;3(2):86-96. [\[CrossRef\]](#)
33. Fowlkes JL, Thraillkill KM, Liu L et al. Effects of systemic and local administration of recombinant human IGF-I (rhIGF-I) on de novo bone formation in an aged mouse model. *J Bone Miner Res*. 2006;21(9):1359-1366. [\[CrossRef\]](#)