

Intratympanic Corticosteroid for Neurosensorial Hearing Loss Treatment

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1. Introduction

The application of drugs through the eardrum and into the middle ear to treat various otologic disorders, such as Meniere's disease and sudden sensorineural hearing loss has recently gained widespread popularity. The intratympanic treatment modality can provide also a chemoprotection strategy for exposure to noise (1) cisplatin (2), and aminoglycosides (3).

Inflammatory processes may play a role in the etiology of various inner ear pathologies of which the pathogenesis is poorly understood. Intratympanic corticosteroid may be a promising therapy for several ear disorders.

Neurosensorial hearing loss therapy to date has consisted mostly of the systemic administration of steroids and has been limited by their side effects and low therapeutic concentrations within the fluids and tissues of the inner ear. It has been shown in animals and humans that systemically applied glucocorticoids reach only low drug concentrations in the perilymph. The local application of drugs to treat inner ear diseases is expected to provide advantages as compared with systemic treatments, namely: 1) bypassing the blood-labyrinthine barrier, 2) resulting in higher concentrations in the inner ear fluids 3) avoiding major unwanted effects of systemically administered medications.

Despite some successes, the local medical treatment of inner ear conditions, is often frustrating to patients and physicians. We review the status of the intratympanic corticosteroids treatment.

2. History

The delivery of medications to the inner ear through the transtympanic route dates back to 1935, when Barany (4) used intratympanic lidocaine for treatment of tinnitus. Since then, other molecules have been used and the indications have expanded. In 1948, streptomycin was used to treat patients with unilateral Meniere's disease specifically on the basis of its vestibulotoxic effects (5). It was Harold Schuknecht who proposed the use of streptomycin as an alternative to surgical unilateral labyrinthine ablation (6). Francis Bauer, in 1969 and 1971 reported on the treatment of "Glue Ear" by using intratympanic urea (7). Another

interesting application of intratympanic medication was reported by Bryan in 1973, when he described the use of intratympanic steroids in a patient with facial paralysis (8). Itoh (9), in 1991, used steroids for Meniere's disease. Silverstein (10) in 1996, used steroids for Sensorineural Hearing Loss.

3. Anatomy

The cochlea can be thought of as a long coiled tube looking much like a snail shell (11). It is composed of three compartments. The middle compartment is the scala media, which is filled with endolymph. The lower and upper fluid compartments respectively are the scala tympani and scala vestibuli, both of which are filled with perilymph. These two compartments communicate with each other at the apex of the cochlea through the helicotrema. The round window is a membranous opening in the bone within the scala tympani. It sits at the base of the scala tympani and is very compliant, capable of bulging into the middle ear. It separates perilymph from the middle ear space. The oval window, in the scala vestibuli, contains the footplate of the stapes, one of the middle ear bones, that transmits acoustic vibrations from eardrum to the inner ear.

4. Physiology

Most of the structures of the cochlea are protected from the systemic circulation by the presence of a blood-cochlear barrier (or blood-labyrinthine barrier), similar to the blood-brain barrier. There is exchange between the different compartments of the inner ear: between tympanic perilymph and vestibular perilymph and between endolymph and perilymph. But also between the inner ear fluids and cerebrospinal fluid and between the inner ear fluid and plasma (12) (13). Exchanges between endolymph and plasma are through the stria vascularis and between perilymph and plasma through the capillaries perilymphatic. At this level makes a pass filtering products: blood-labyrinthine barrier (13).

This blood-inner ear barrier consist of tight junctions and other mechanisms that limit access of molecules to inner ear targets. In fact the endothelial cells are connected with tight junctions and without fenestrations (14). This network of tightly coupled endothelial cells is the dominant component of the blood-cochlear barrier which make this solid barrier impermeable to macromolecules. In addition to this physical barrier, there is a chemical barrier between blood and endolymph/perilymph wich has a selectivity to electrolytes and water-soluble molecules (15).

In the fluid of the inner ear, there are other obstacles to the spread of drugs administered systemically: Because the scala media has a relatively high positive charge due to the endocochlear potential, the charge the drug carries will be a significant factor in its ability to enter the scala media, with positively charged drugs at a disadvantage (13).

The relatively high protein content of perilymph will tend to bind drugs (16). Protein interactions with drugs are as important in the perilymph as in blood. Albumin levels are high and can bind acidic drugs, and acid glycoproteins can bind basic drugs (16). Partition coefficients of drugs with these proteins will determine free concentration of the drug. The free fraction of the drug binds to the sensory cells and exerts its effect (13).

The cochlea is surrounded by the petrous bone. It was shown that there is a direct exchange between the extracellular space of the petrous bone and perilymph through the lacuna canaliculi which are canals or holes in the bone in free communication with the scala tympani (17).

5. Pharmacokinetics and pharmacodynamics

Treatment given by intratympanic will diffuse in liquid of the inner ear. There are 3 practical entry points: 1) through round window membrane RWM (at the base of the cochlea on the scala tympani side), 2) through or near the oval window (at the base of the cochlea on the scala vestibuli side), 3) through the bone of the cochlea via application in the middle ear. This infusion is mainly through the round window.

The RWM has three layers (18): an outer epithelial layer on the middle ear side, a middle fibrous layer, and another epithelial layer facing the inner ear. The outer epithelial layer contains some microvilli and abundant mitochondria, suggesting that it may be able to absorb substances and carry out metabolic activities. The inner epithelial layer has areas of discontinuous basement membrane that may provide space for substances to traverse the membrane.

Plontke (19), and colleagues have extensively modeled the distribution of drugs applied at the RWM. They suggest that in addition to diffusion along the length of the cochlea, diffusion through the tissue of the cochlea from one scala to another must be considered as well.

Some factors facilitate the passage of molecules through the round window membrane: low molecular weight, water-soluble nature, the ionic charge, histamine, prostaglandins, leukotrienes, endotoxin of *E. coli*, Staphylococcus exotoxins (20). The contact time with the round window membrane has the most important effect. Wang (21) demonstrates that the inner ear pharmacokinetic profile of steroids administered intratympanically is dependent upon the nature of the vehicle as well as the physicochemical properties of the steroid drug itself. In fact the degree of aqueous solubility of the drug has a major impact on its residence time and exposure in the inner ear (21).

Glucocorticoid receptors have been identified in the inner ear and are more abundant in the cochlea (22). The presence of glucocorticoid receptors in the inner ear provides a cellular means by which circulating glucocorticoids can directly affect the inner ear physiology. Corticosteroids have been used extensively for inner ear disease because of their anti-inflammatory effects but also affect the vascularity of the inner ear. Corticosteroids have many effects : they prevent a decrease in cochlear blood flow, reduce degeneration of the stria vascularis and have an antioxidant effect (23).

6. Choice of drug

Two corticosteroids are used by the majority of the researchers: dexamethasone and methylprednisolone. The concentration is varied between 4 mg/ ml and 25 mg/ml for dexamethasone and between 32 mg/ ml and 62,5 mg/ml for methylprednisolone.

Parnes in pharmacokinetic animal study compared intracochlear levels of three glucocorticoids: dexamethasone (Dexa), methylprednisolone (MP), and hydrocortisone

(24). When correcting for the lower Dexa concentration (4 mg/mL) compared to MP (40 mg/mL) in their study and for the higher potency, dexamethasone is expected to reach higher effective levels in perilymph after application to the round window membrane. In addition, contrary to Dexa, MP solution is not stable but hydrolyzed after some days in the pump cartridge (19) (25).

7. Intratympanic delivery methods

There is no standard protocol for IT corticosteroid injections; the frequency of injections, concentration and type of corticosteroid. Method of injection is determined by the individual surgeon.

Multiple intratympanic delivery methods are described:

Syringe delivery is a simple method. However, direct injections do not allow for prolonged delivery. We can anesthetize the tympanic membrane with 10 percent Xylocaine. A drop of phenol on the ear drum is one method. Another is a topical anesthetic such as "Emla" cream. The drug is injected, left in the middle ear for 30 minutes.

The myringotomy is placed in the most superior and anterior location to allow maximal filling of the middle ear space with the corticosteroid solution while the patient is supine. Placement of the tube eliminates the need for a new myringotomy for each subsequent injection. For injection, we use a 25-gauge spinal needle attached to a 1-mL tuberculin-type syringe. To equalize pressure, two needle punctures were made in the anterior superior quadrant of the tympanic membrane, the first for injection and the second (superior) for air escap. The initial injection was followed by a second injection about 15 minutes later for a total volume of approximately 0.5 mL. The patient remained supine for 30 to 40 minutes, with the head turned to the side and the injected ear upright, and was instructed to swallow as little as possible to help maintain the fluid in the middle ear space for longer duration.

Microwick is the polyvinyl acetate wick (1 mm diameter by 9 mm length). It absorbs medication and transports it directly to the RWM. It's placed through a tube, at the round window niche. It allows instillation by the patient himself at home. The MicroWick should be removed or replaced after 4 weeks of treatment to prevent it from becoming adherent to the mucosa of the round window (26).

Microcatheter is composed of two tubes: one for injection and the other for the return of excess liquid. It ends with a bulge that is placed at the round window niche under general anesthesia. Some researchers propose to link the catheter to a pump. This would allow continuous irrigation and delivery of the product constantly at the round window.

8. Indications

Corticosteroids are indicated in several types of sensorineural affects. Indications are : sudden deafness, autoimmune Deafness, Deafness and Dizziness related to Meniere's disease and Tinnitus.

They are also available for otoprotection against physical and chemical aggressions of the inner ear. It seems that corticosteroids will respond to inner ear hair cells and nerve cells. They may prevent, limit and recover the damage caused by noise trauma (27). They may be

given in anticipation of ototoxicity that could be associated with systemic aminoglycoside antibiotic or cisplatin and other chemotherapeutic agents. They can also be used after injuries (28).

9. Results

Intratympanic corticosteroids for sudden hearing loss and Meniere's disease has been the subject of retrospective, uncontrolled studies and a few controlled studies with small numbers of subjects. Hamid in 2001 with a single injection of high concentration of Dexamethasone (24mg/ml) for patients with Meniere's disease, was able to get control of vertigo in 90% of cases with an improvement of hearing threshold, the percentage of discrimination and sensation of fullness (29) (26). In his study, 90% of patients had vertigo control, 90% had improved speech discrimination, and 90% had decreased aural pressure.

Garduno (30), compared intra tympanic Dexamethasone versus placebo in Meniere disease. He obtained full control of vertigo in 82% of cases against 57% with placebo with significant differences. He also noted a reduction of tinnitus in 48% of cases and hearing improvement in 35% of cases.

In sudden deafness, Ahn (31) compared two groups: systemic corticosteroids alone versus intratympanic corticosteroids associated with systemic treatment. He found no significant difference in overall response, but noted a significant improvement on the low frequencies in intratympanic treatment group. HONG (32) compared intratympanic corticosteroids alone versus systemic corticosteroids alone also found no difference, but noted a significant improvement over the low frequencies. Alatas (33) concluded that intratympanic dexamethasone is an effective therapy for low frequency hearing loss. Hunchaisri (34) concluded that it may have benefits for patients with sudden sensorineural hearing loss who failed systemic steroid therapy.

In diabetic patients with sudden sensorineural hearing loss, intratympanic corticoid injection is as effective as systemic steroid treatment and it can avoid undesirable side effects (35). Han studied three groups of diabetics and compared prednisolone administered by oral, intravenous and intra tympanic Dexamethasone. He noted a better outcome with intratympanic treatment without significant difference. However, systemic treatment was discontinued in 6 patients due to problems of hyperglycemia. This disadvantage is not observed with the intratympanic treatment.

Many studies concluded that using the continuous intratympanic dexamethasone by MicroWick is effective, safe and efficient for treatment of sudden idiopathic sensorineural hearing loss (26) (19).

There is an increasing number of series evaluating intratympanic (IT) steroids as first line or salvage therapy in ISSHL with some studies presenting control groups and randomized controlled trials (Table 1).

The effect of intratympanic corticosteroids on tinnitus is difficult to assess due to limited work. Shulman (37) treated tinnitus with intratympanic dexamethasone and obtained control of tinnitus in 50% cases (for 1 year and over).

Author	Type of study	Steroid used	Protocol	Results
Gianoli (48)	prospective		salvage treatment Steroids through a ventilation tube 4 separate occasions over the course of 10 to 14 days	Hearing improvement in 44%
Xenellis (49)	Randomized controlled study	Methylprednisolone	salvage treatment 40 mg/mL 4 times within a 15-day period	Significant improvement
Haynes (36)	retrospective	Dexamethasone	24 mg/mL	27.5% showed improvement (≥ 20 dB)
Ahn (31)	controlled study	Dexamethasone	0.3 mL on days 1, 3, and 5	Total recovery rate was 73.3% and 70.0% in the control group better hearing improvement at 250 Hz than the control group
Hong (50)	Randomized controlled study	Dexamethasone	Primary treatment 5mg/ml once a day for eight days	hearing recovery rate compared with patients treated with oral steroids improvement at low frequencies
Han (35)	Prospective, nonrandomized multicenter clinical trial	Dexamethasone	SNHL with diabetes four times within a two-week period	no significant difference with systemic treatment no patients who failed to control their blood sugar level
Lee (51)	retrospective	Dexamethasone	salvage treatment 5 mg/mL, six injections over 2 weeks	significant improvement for severe SNHL

Author	Type of study	Steroid used	Protocol	Results
Kara (52)	Prospective control	Dexamethasone	5 intratympanic injections with the dose of 4 mg/ml,	Intratympanic steroids gave better hearing results than systemic steroids with no systemic side effects
Plontke (19)	Randomized, double-blind, placebo controlled multicenter trial.	Dexamethasone	4 mg/ml continuously applied for 14 days	better hearing improvement in the treatment group absence of serious adverse events

Table 1. Review of Literature on Intratympanic steroid Therapy for sudden neurosensorial hearing loss

The effectiveness of steroids in reducing noise induced hearing loss has been inconclusive (13). Many types of steroids, antioxidants and growth factors have been studied to protect the ear from trauma or to minimize or reverse damage (38) (39). Some researchers have used antioxidants such as D-methionine and N-acetylcysteine to prevent noise induced hearing loss (40). A variety of growth factors and peptides, are being introduced to combat the effects of Noise induced hearing loss : Insulin-like growth factor-1 (IGF-1), neurotrophic factor-3 (NT-3) , AM-111 and D-JNKI-1 peptides (41) (42) (40).

Steroids have also been tested for their otoprotective attributes during antibiotic treatment. The intracochlear infusion of dexamethasone before and after kanamycin delivery protected hearing (43). Hill (44) concluded that IT dexamethasone may be a safe, simple and effective intervention that minimizes cisplatin ototoxicity without interfering with the chemotherapeutic actions of cisplatin.

A sudden or progressive hearing loss can occur during radiation treatment of head and neck tumors (45). Patients are commonly given steroids to reduce inflammation, but their local delivery would reduce the side effects associated with systemic steroid treatment (13). Inflammation often results from inner ear surgical trauma, as well (46).

10. Complications

Complications of intratympanic injections of corticosteroids are uncommon and banal (19). Those most often reported in the literature are: 1) some individuals experience intense pain during injection, 2) vertigo and tinnitus, 3) Other complications are rare and include acute otitis media and mastoiditis.

Patients who undergone trans-tympanic aerator to avoid multiple injections or to put in the microwick have an increasing risk of persistent eardrum perforation (47). In fact, 20% of these patients had non healing perforations that needed repair using a fat graft (26).

11. Conclusion

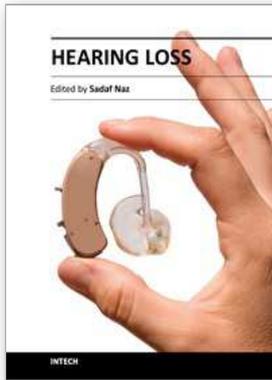
The intratympanic treatment has several advantages. It is an effective procedure for the control of cochleovestibular disorders such as sudden deafness and Ménière's disease. Up till now, there is no consensus on the IT protocol. Future studies will define the best prctocol. The perspective is the development of the gene therapy and the intracochlear treatment.

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Authored by 17 international researchers and research teams, the book provides up-to-date insights on topics in five different research areas related to normal hearing and deafness. Techniques for assessment of hearing and the appropriateness of the Mongolian gerbil as a model for age-dependent hearing loss in humans are presented. Parental attitudes to childhood deafness and role of early intervention for better treatment of hearing loss are also discussed. Comprehensive details are provided on the role of different environmental insults including injuries in causing deafness. Additionally, many genes involved in hearing loss are reviewed and the genetics of recessively inherited moderate to severe and progressive deafness is covered for the first time. The book also details established and evolving therapies for treatment of deafness.

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