Intratympanic Perfusion for Treatment of Meniere's Disease

Mohamed Abdelmohsen Alnemr, Amira Selem Abdelazem Selem, Ezzeddin Mohamed Elshiekh, and Alaa Eldin Mohamed Elfeky
Otorhinolaryngology Department, Faculty of Medicine - Zagazig University
Corresponding Author: Amira Selem Abdelazem Selem
Email: amiraselem25@gmail.com

Abstract

Background: Ménière's disease, defined by Prosper Ménière at the beginning of 19th Century, is a syndromic inner ear disease which is commonly associated with a pathological accumulation of endolymphatic fluid in the inner ear "idiopathic endolymphatic hydrops".Endolymphatic hydrops (EH) seems to be due to an overproduction of endolymph and/or a decrease in the absorption of endolymph. Endolymphatic pressure variations may result from alterations in secretion, osmosis, and resorption.EH is a pathological condition in which there is a distention of the scala media by enlargement of endolymphatic volume (19) with ballooning of Reissner's membrane into the scala vestibule from its flat configuration due to endolymphatic pressure elevations. Induced tension can return the membrane to its normal position if the displacement is mild and the pressure is physiological and transient.When first-line treatment does not offer a satisfactory symptoms control, especially for vertigo, more invasive treatments (the second line) must be considered. The second line is the intratympanic injections, mainly intratympanic steroid (ITS) as a conservative treatment and intratympanic gentamicin (ITG) as a destructive treatment. After this second line, 90 to 95% of the patients are cured or in remission.

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Introduction

Ménière's disease, defined by Prosper Ménière at the beginning of 19th Century, is a syndromic inner ear disease which is commonly associated with a pathological accumulation of endolymphatic fluid in the inner ear "idiopathic endolymphatic hydrops". Endolymphatic hydrops (EH) seems to be due to an overproduction of endolymph and/or a decrease in the absorption of endolymph. Endolymphatic pressure variations may result from alterations in secretion, osmosis, and resorption **(1).**

EH is a pathological condition in which there is a distention of the scala media by enlargement of endolymphatic volume **(2)** with ballooning of Reissner's membrane into the scala vestibule from its flat configuration due to endolymphatic pressure elevations. Induced tension can return the membrane to its normal position if the displacement is mild and the pressure is physiological and transient **(1)**

Light microscopy showed no structural alteration in cochlear sensory hair cells and innervation patterns that could account for the symptoms of MD so the underlying pathophysiology is probably biochemical or ultra-structural in nature. A detailed ultra-structural study of a temporal bone using serial

electron microscopy in a patient with unilateral MD showed a considerable decrease in afferent synapses at the base of both the inner and the outer hair cells in the ear with MD compared with the contralateral ear **(3).**

Histological analysis of the endolymphatic sac in an extensive series of human temporal bones consistently revealed pathological changes in cases with idiopathic endolymphatic hydrops, but no such changes were found in cases with secondary endolymphatic hydrops due to other otological diseases or in healthy controls **(4).**

Histopathology of the human temporal bone has been used to recognize the intrinsic pathological changes that might cause MD. Studies assessing the distribution of EH in specimens obtained after death from patients with MD revealed the universal involvement of structures of the inferior parts of the inner ear (the saccule and the cochlea), with less frequent involvement of the superior sections (the utricle and the semicircular canals) **(3).**

Anatomical variations of the temporal bone include changes in the anatomy and positioning of the vestibular aqueduct, endolymphatic duct and sac, and the lateral (sigmoid) sinus, and pneumatization of the petrous bone. These factors potentially predispose to MD. Exaggerated narrowing of the isthmus of the endolymphatic duct is a histopathological feature more commonly observed in the temporal bone of MD patients **(3).**

MD is a complex ,heterogeneous disorder in which several underlying factors interact, including anatomical variations in the temporal bone, genetics, autoimmunity, migraine, altered intra-labyrinthine fluid dynamics and cellular and molecular mechanisms **(3).**Several lines of epidemiological evidence support a genetic contribution in MD including the higher prevalence observed in the European population over other cities, and a strong familial aggregation found in Europeans and South Koreans ranging from 6% to 10% of cases with a high sibling recurrence risk ratio **(23).**

Ménière's disease showed comorbidities with several disorders including autoimmune diseases and migraine **(1).** Migraine is considered to be one of the most important cofactors in MD, but other disorders are also strongly linked with vertigo attacks **(3).**

The majority of Ménière's disease cases are considered sporadic, although familial aggregation has been recognized in some cases. Repeated exposure of hair cells to toxic levels of a K^+ enriched perilymph, the overpressure itself, and the sudden rupture of distended membranes explain the long-term vestibular and auditory damage in MD **(5).**

The diagnostic criteria for MD were revised in 2015 by a Joint Consensus agreed on by five international scientific societies: The Barany Society, The Korean Balance Society, The Japan Society for Equilibrium Research, The European Academy of Otology and Neurotology, and the Equilibrium Committee of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HSN). Two diagnostic categories were accepted: definite MD and probable MD **(6).**

The main clinical aspect in MD is the recurrence of sudden and unexpected vertigo attacks that are often debilitating and may severely affect quality of life. There are many therapeutic options for MD, but none is considered effective by the scientific community **(6).**

The first line of treatment includes the medical conservative treatment. After this line of treatment 80% of patients with MD are cured or in remission **(7).**

When first-line treatment does not offer a satisfactory symptoms control, especially for vertigo, more invasive treatments (the second line) must be considered.

- The second line is the intratympanic injections, mainly intratympanic steroid (ITS) as a conservative treatment and intratympanic gentamicin (ITG) as a destructive treatment. After this second line, 90 to 95% of the patients are cured or in remission **(7).**

Intratympanic injection therapy has been very popular and widely used since the last two decades as being practical to apply even in the office setup.

The vestibule of the inner ear is a crucial drug delivery target for the treatment of balance disorder. There are two permeable openings from the middle ear into the internal ear - the round window and the oval window **(8).** Routes for drug entry into the inner ear include the systemic circulation and the round window membrane (RWM), which connects the middle ear with the inner ear **(9).**

Drug delivery to the inner ear can be achieved by systemic administration, but limited local blood supply and poor penetration of the blood-perilymph barrier, which restricts entry of most blood-borne compounds into internal ear tissues and results in subtherapeutic local concentrations so administration of large doses of medication is required to produce the desired therapeutic effect leading to severe vestibular and cochlear toxicities **(8).** To reduce the adverse effects of systemic drug delivery, more localized intratympanic drug delivery systems were developed to target inner ear disease. Drug concentrations measured in the inner ear fluids, perilymph and endolymph, are significantly higher with intratympanic injection than with oral or parenteral administration **(9).** The risks of vestibular and cochlear toxicity of gentamicin are related to the age, the duration of the therapy, the total or cumulative dose, individual susceptibility, renal function, and associated inner ear problems, like noise exposure or autoimmune disorders **(10).**

The RWM is semi-permeable membrane and covered by three layers. It is a continuation of the mucous membrane lining the middle ear (outer cuboidalepithelial layer) followed by middle fibrous layer, and an inner mesothelialepithelial layer. The RW niche favors retention of substances at the RWM. Low blood flow rates and a limited passage through a blood-labyrinth barrier interfere with systemic application of drugs, so a local administration appears attractive **(11).**

Drug dispersal into the inner ear depends on multiple factors, including RWM permeability, the rate of drug diffusion within the perilymph, the concentration of gentamicin, and the frequency of application (the clearance of gentamicin from the inner ear takes days after a single injection) **(9).**

RWM permeability from the middle ear depends upon liposolubility, molecular weight,concentration and amount injected, electrical charge, albumin concentration, toxins, anesthetics, antibiotics, local biochemical mediators (prostaglandins, leukotrienes and histamine), RWM thickness, and presence of RWM inflammation or injury or fibrosis. Small cationic particles preferentially pass through the RWM. Histamine has been shown to facilitate uptake of intratympanic injected dexamethasone **(9).**

In early stages of middle ear inflammation, RWM permeability increases. In later stages of infection (round window niche adhesions or plugs, granulation tissue formation), RWM becomes thick so RWM permeability decreases to protect inner ear function. Inflammation secondary to topical application of saline or hydrocortisone can lead to local edema and membrane leakage of the RWM, which in turn increases RWM permeability **(9).** Uptake of

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substances and particles from the middle ear cavity is seemingly decided by the mucosal epithelial cells and mainly a selective and active process **(11).**

Intratympanic corticosteroid is an effective treatment for Ménière's disease. Among the two available steroids derivatives, dexamethasone is practical to use due to better tolerance by the patients, as methylprednisolone creates burning sensation in the middle ear mucosa. Intratympanic methylprednisolone can improve hearing level to a greater extent than intratympanic dexamethasone, but the two groups were similarly beneficial in controlling vertigo **(11).** Corticosteroids have been shown to have a lower risk of hearing damage but a less efficacy in vertigo attack control compared to gentamicin **(6).**

Gentamicin is an aminoglycoside antibiotic having more vestibulotoxic than cochleotoxic effect. Its effect is mainly causing atrophy on type 1 vestibular cells as well as the neuroepithelium. ITG administered in different doses and timing has been proven as an effective treatment for vertigo in MD with some risk of hearing loss **(6).** The hearing did not change in some patients. Some showed a certain degree of hearing improvement, while others showed the hearing deterioration **(10).** ITG showed the greatest treatment effect, as represented by larger reductions in both self-reported vertigo episodes and work absenteeism **(12).**

Controversy remains about the gentamicin dosage and method used. Some physicians favor the use of low-dose gentamicin in which the drug is injected once and further injections are only performed in cases of recurrent vertigo attacks; other authors prefer high-dose gentamicin, titration or continuous administration in which the drug is injected until vestibular weakness is reached **(3).** Due to the toxic effect of ITG over the peripheral vestibular end-organ, dizziness and unsteadiness following the injection can be resolved by vestibular rehabilitation.

The inner ear toxicity of gentamicin follows an order. Secretory dark cells of the vestibule are the first to be damaged, followed by the vestibular neuroepithelium then, the hair cells of the organ of Corti. The dose in each injection and the time interval between two doses are two factors to be solved. The initial reversible effect of gentamicin on both the vestibule and cochlea may become an irreversible due to the accumulation of consecutive doses due to gentamicin slow clearance from the inner ear **(10).**

Because of the horizontal, slightly elevated position of the patient's head during ITG injection, the lateral semicircular canal is the most sensitive to gentamicin and the first one to be ablated. On the other hand, because of gravity, the superior semicircular canal is expected to be ablated last **(13).**

In Patel et al.'s study, 30 patients with Ménière's disease were injected by gentamicin (40 mg/mL) 2 weeks apart, and were followed up for 2 years. The mean number of vertigo attacks in the final 6 months of the follow up compared with the 6 months before the first injection decreased by 87%. 8 Patients did not improve vertigo after 1st injection, and were needed additional injections. Three patients reported one adverse event after ITG. One of them was ear infection **(5).**

In Kontorinis et al.'s study, 0.6–0.8 mL of 40 mg/mL gentamicin solution was injected into the middle ear via a 22-G spinal needle under topical anaesthesia using a surgical microscope. The number of injections required ranged from two to three times with 1-week interval **(13).**

Chen et al. used One ml of 40 mg/mL gentamicin solution, drawn into a 1 cc tuberculin syringe that was fitted with 25-G spinal needle in the treatment of MD patients by a single dose administered. Patients were evaluated 4 weeks

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after ITG. Approximately 70% exhibited the expected disequilibrium caused by the gentamicin and were considered adequately treated. Those who return for 4-week follow-up and had no experience of labyrinthine upset were recommended to have a second dose. Patients with good initial treatment response might need repeated ITG if vertigo recurred. Standard vestibular testing includes video- or electronystagmography (VNG/ENG), rotary chair testing. With disease progression, VNG/ENG and rotary chair test should reveal decreasing peripheral vestibular function in the affected ear. VNG/ENG is more sensitive for inner balance dysfunction, but rotary chair test is more specific **(30).**

In Carey et al.'s study, 17 MD patients was injected by 0.4 ml of 26.7mg/ml of gentamicin. 9 patients repeated ITG at weekly intervals until patients developed spontaneous nystagmus, post head shaking nystagmus or a head thrust sign. 5 patients developed theses signs after a single injection, 2 patients developed signs after 2 injections, and 2 patients developed signs after 3 injections. 8 patients were injected once and assessed 3 weeks later to determine if they had unilateral vestibular function ablation. Complete vertigo control was obtained after a single injection in 7 of the 8 patients. The non-responder patient was injected 2 times more at interval of 3 and 2 months until vertigo was controlled **(7).**

In Pietro et al.'s study, 77 MD patients were injected by 27.6 mg/ml of gentamicin (2ml of gentamicin sulfate (40mg/ml) buffered with 1ml of sodium bicarbonate to obtain 6.4 PH). 35 patients were injected with high dose (total 6 injections, twice daily, repeated every 3 days), and 42 patients were injected with low dose (1-2 injections) and evaluated after 7, 14, and 21 days to assess treatment outcomes. The 2nd injection was planned 20 days after the 1st injection **(15).**

In Kaplan et al.'s study, 114 patients were injected 3 times a day for 4 consecutive days with 93.4% of vertigo control and 25.6% of hearing loss **(10).**

Stanley et al study compared the effectiveness of five different techniques of ITG for vertigo control in MD patients **(16).**

i. Seven studies described the multiple daily ITG (three times per day).
ii. Two studies described the weekly ITG (weekly injections for four total doses).
iii. Eight studies described the low-dose ITG (one to two injections with subsequent injections for recurrent vertigo).
iv. Four studies described continuous microcatheter delivery.
v. Six studies described the titration technique (daily or weekly injection until onsets of vestibular symptoms, vertigo control, or hearing loss were detected).

- The titration method of ITG demonstrated significantly better complete vertigo control (81.7%, $p = 0.001$) and better effective vertigo control (96.3%, $p < 0.05$) compared with other techniques, and the low-dose ITG demonstrated significantly worse complete vertigo control (66.7%, $p < 0.001$) and worse effective vertigo control (86.8%, $p = 0.05$) compared with other techniques.
- The weekly ITG demonstrated less overall hearing loss (13.1%, $p = 0.08$), and the multiple daily method demonstrated significantly more overall hearing loss (34.7%, $p < 0.01$) compared with other techniques.
- No significant difference in profound hearing loss was demonstrated between techniques.
- Degree of vestibular ablation of ITG was not significantly correlated with the vertigo control or hearing loss.

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Titration methods or multiple injections on a daily basis can be preferred if the patients have profound or non-serviceable hearing, as they have significant incidence of hearing loss. ITG with a frequency longer than once every week, or with injections on a monthly basis as "needed" provide the same level of vertigo control with better hearing conservation **(10).**

Clinical Advantages of Intratympanic Injection **(8);**

- No systemic side effects due to no systemic absorption.
- Higher local concentration compared to systemic administration as it avoids first-pass metabolism.
- Low morbidity.
- The procedure is generally well-tolerated.
- Relatively easy to perform as an outpatient procedure requiring only topical local anesthesia.
- Low cost.

Signs of vestibular impact **(10).**

- ✓ Spontaneous and head-shaking nystagmus that was not present before the treatment confirmed ITG effectiveness. Casani et al reported that these signs could be obtained within days after only 1 injection in 81% of patients **(10).**
- ✓ Caloric response: Most of MD patients may already have a reduced caloric response on the affected side before ITG. A decrease in the caloric response is expected after ITG. The absence of caloric response after the last ITG injection demonstrates permanent acute vestibular deafferentation. The aim of ITG should be vertigo control with preservation of the caloric response **(10).**
- ✓ Head thrust test (HTT): Gentamicin therapy is associated with vestibulo-ocular reflex deficit during rapid head movements. A positive head thrust test is a prognostic indicator, even after a single ITG injection, and a reliable sign of the effect of ITG on vertigo control **(10).**HTT is a valuable simple clinical test that is predictive of the durability of the ITG treatment benefit, and requires no specialized equipment **(17).**
- ✓ Vestibular-evoked myogenic potentials: Picciotti et al reported that all normal vestibular-evoked myogenic potential responses disappeared after ITG, the caloric response was absent in 50%, and caloric test-induced asymmetry was observed in the remaining patients **(10).**
- ✓ Electronystagmography: ENG evaluates the vestibular system to determine if balance problems originate from central or peripheral nervous system. The ENG may be performed using videonystagmography (VNG), which uses video cameras to record eye movements. ENG and VNG record spontaneous or induced nystagmus. Caloric test is one of the ENG tests (34). We used VNG/ENG in our study which is sensitive for inner balance dysfunction **(14).**

Caloric testing seems not to be an ideal tool to analyze the correlation between vertigo control and the effect of ITG as compared with gain asymmetry of the vestibulo-ocular reflex. Vestibular-evoked myogenic potentials and the head thrust test are more reliable than other vestibular tests for the follow-up of vertigo control in patients undergoing ITG **(10).**

None of the patients treated with ITG had any contralateral abnormal responses **(13).** ITG has received more interest due to its strong effect on vertigo control in MD patients, which also beat the frequency of vestibular neurectomies **(18).**

ITG and labyrinthectomy can ablate the vestibular function; however, ITG has the significant advantage of expected hearing preservation.

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The third line is the surgical, conservative or destructive, treatment **(7).** Vestibular neurectomy is a selective technique issued to superior and inferior vestibular nerves and keeping the cochlear nerve safe. Labyrinthectomy is the oldest surgical method to treat MD, and today is limited to older patients with unserviceable hearing **(18).**

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