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Dexamethasone Inner Ear Perfusion by Intratympanic Injection in Unilateral Ménière's Disease: A Two-year Prospective, Placebo-Controlled, Double-blind, Randomized Trial

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OBJECTIVE: To investigate the efficacy of dexamethasone inner ear perfusion by intratympanic injection in hearing loss, tinnitus, aural fullness, and vertigo in the treatment of unilateral Ménière's disease and compare it with the control group.

STUDY DESIGN AND SETTING: A prospective, randomized, double-blind study with 2-year follow-up comparing changes secondary to dexamethasone inner ear perfusion versus placebo consisting of saline solution.

PATIENTS: Twenty-two patients having definite Ménière's disease as outlined by the 1995 American Academy of Otolaryngology–Head and Neck Surgery Committee on Hearing and Equilibrium. All the patients were older than 18 years of age and were not receiving any other form of treatment with steroids for their Ménière's disease.

METHOD: Five consecutive daily intratympanic injections of dexamethasone or placebo to the involved ear.

RESULTS: In the dexamethasone group at 2-year follow-up, complete control of vertigo (class A) was achieved in 9 of 11 patients (82%) and substantial control of vertigo (class B) in the remaining 2 patients (18%.) In the control group only 7 of 11 patients (64%) finished the 2-year follow-up because in the other 4 patients (36%) we had to give another treatment for the continuing vertigo and thus they were classified as failure (class F.) From the 7 patients who have finished the follow-up of 2 years in the control group, 4 patients (57%) achieved class A, 2 patients (29%) achieved class C, and 1 patient (14%) class F.

CONCLUSIONS: Dexamethasone (4 mg/mL) inner ear perfusion in a group of patients with unilateral Ménière's disease (Shea's stage III) showed 82% of complete control of vertigo over placebo (57%). There was also a subjective improvement in tinnitus (48%), hearing loss (35%), and aural fullness (48%) in the dexamethasone group compared with 20%, 10%, and 20% respectively in the control group.

EBM Rating: A

We prefer to use the term "dexamethasone inner ear perfusion (DIEP) by intratympanic injection" because that is exactly what we are doing, where intratympanic refers to the route of administration that we realized by injection and inner ear perfusion refers to the type of therapy performed. Therefore intratympanic therapy is a misinterpretation of the term, because we are not giving therapy to the tympanic cavity; in fact, we are applying an injection intratympanically in order to perform inner ear perfusion. Actually, tympanic comes from the Latin *tympanicus*, which means relative or belonging to the tympanum. And tympanum comes from the Latin *tympanum* and this from the Greek týmpanon which means tympanic cavity, medium ear, and, less correctly, tympanic membrane.

Since McCabe demonstrated the role of aggressive steroid treatment of certain inner ear diseases in the description of autoimmune sensorineural hearing loss,[1] there has been an ever-increasing body of clinical and laboratorial evi-

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dence that Ménière's disease is evidenced as an immune-mediated disorder of a small, misplaced, and malfunctioning endolymphatic sac. Elevated levels of IgG circulating immune complexes,[2-4] autoimmune response to type II collagen,[5,6] focal inflammation with intraepithelial invasion by mononuclear cells recognized as "endolymphatic sacitis" by Danckwardt-Lilliestrom,[7] IgG deposits in endolymphatic sac,[8] and the demonstration of autoantibodies to the endolymphatic sac[9] have been implicated in relation to immunological abnormalities as a cause of Ménière's disease. Experimental descriptions of corticosteroid receptors within the inner ear and histological changes to the stria vascularis by corticosteroids[10] have demonstrated a crucial role of corticosteroids in the inner ear physiology. Also, Rarey and Curtis[11] identified receptors in both the cochlear and vestibular tissues, with the highest concentration of receptors found in the spiral ligament. Lohuis[12] demonstrated that the cellular structure of the stria vascularis underwent atrophy after removal of adrenal steroids. These findings gave strength to the conviction of using steroids to treat inflammatory inner ear disorders, whether systemically or intratympanically, and that there is a role for steroids in the maintenance of normal functions of the stria vascularis. Systemic steroid administration has been proved with success and is one of the current standard treatment options. Dexamethasone is one of the most potent corticosteroids, is the longest acting, and causes the least sodium retention. The potential risks of systemic corticosteroids, in particular the risk of avascular necrosis of the femoral head, have received much attention in the recent medicolegal field. It seems reasonable that the local therapy with dexamethasone avoids all other disruptive secondary effects like susceptibility to infection, diabetes, osteoporosis, peptic ulcer, hypertension, psychological changes, myopathy, ocular effects, and impaired wound healing.[13]

The rational use of the inner ear perfusion was sustained in the semipermeable capability of the round window membrane. The drug deposited locally in the middle ear cavity is transported by pinocytosis through the outer layer of the round window membrane, where the micropinocytic vesicles containing the drug are transported to the connective tissue of the middle layer, from here reaching the perilymph by lymphatic and blood vessels or crossing the inner layer directly to diffuse into the perilymph. Other routes of entry include the oval window annular ligament and the small lacunar mesh in the bone wall surrounding the inner ear.

Chandrasekhar[14] demonstrated that within an hour after administration of intratympanic dexamethasone in a guinea pig model, results show significantly higher perilymph concentrations than intravenous dexamethasone. Furthermore, Parnes[15] reported evidence that cortisone, methylprednisolone, and dexamethasone accumulate in the perilymph and endolymph in much larger concentrations and remain longer after round window perfusion in the guinea pig than after oral or intravenous administration, with prednisolone having the best profile. Shirwany[16] demonstrated increase in cochlear blood flow that persisted for at least 1 hour, no change in auditory brain stem responses, and no histologic changes with the acute use of intratympanic injection of dexamethasone in guinea pigs. As a result of these advances, steroids have been used in Ménière's disease in order to decrease this immunological reaction.

In this investigation we studied the efficacy of dexamethasone inner ear perfusion through an intratympanic injection on vertigo, hearing loss, tinnitus, and aural fullness in patients with definite Ménière's disease as outlined by the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) Committee on Hearing and Equilibrium in 1995.[17]

METHODS

A prospective, 2-year follow-up investigation was carried out in the Department of Neurotology of the National Institute of Neurology and Neurosurgery in Mexico City between November 2000 and July 2003. Twenty-four patients older than 18 years of age, without any previous medical treatment with steroids or surgery for Ménière's disease, were included in this study. Before the inclusion in this study all the patients failed to respond to conventional medical therapy with caffeine and salt restriction ($<$1500 mg/day), vasodilator, and diuretic given at least 6 months without any relief of vertigo attacks. There was provided a detailed explanation of the procedure, including risks and possible benefits, and a written informed consent was obtained. The protocol was submitted to and approved by the Investigational and Ethical Review Board of the National Institute of Neurology and Neurosurgery.

All the patients were classified at Shea's stage III, in which hearing loss is for all tones, and with poor speech discrimination, but fullness, dizzy spells, and tinnitus are the chief complaints.[18]

All patients underwent pure tone audiogram (PTA), speech reception threshold, and speech discrimination score (SDS).

A change of 10 dB or more in PTA, or 15% or more of change in word recognition score (SDS) as defined by 1995 AAO-HNS, was considered clinically significant.

Also, we applied a subjective hearing improvement scale from 0 to 10, in which 0 was no change and 10 represented 100% of subjective improvement.

Electronystagmography, including vestibular response to caloric stimuli, and extratympanic electrocochleography were also obtained. For vertigo we considered failure only when the patient had to have another definite treatment when vertigo spells lasted 20 minutes or more in spite of the treatment as outlined by 1995 AAO-HNS;[17] in some instances we offered the patient to take a vasodilator or diuretic to support occasional vertigo attacks lasting less than 5 minutes and these were not excluded.

The Dizziness Handicap Inventory (DHI) described by Jacobson[19] was completed in each patient. It consists of 25