Otolaryngology -- Head and Neck Surgery

Induced endolymphatic flow from the endolymphatic sac to the cochlea in Ménière's disease

Marco Mandalà, Liliana Colletti, Marco Carner, Roberto Cerini, Marco Barillari, Roberto Pozzi Mucelli and Vittorio Colletti

The online version of this article can be found at:

Additional services and information for *Otolaryngology -- Head and Neck Surgery* can be found at:

Email Alerts: http://oto.sagepub.com/cgi/alerts

Subscriptions: http://oto.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

>> Version of Record - Nov 1, 2010

What is This?

ORIGINAL RESEARCH–OTOLOGY AND NEUROTOLOGY

Induced endolymphatic flow from the endolymphatic sac to the cochlea in Ménière's disease

Marco Mandalà, MD, Liliana Colletti, PhD, Marco Carner, MD, Roberto Cerini, MD, Marco Barillari, MD, Roberto Pozzi Mucelli, MD, and **Vittorio Colletti, MD,** Verona, Italy

ABSTRACT

OBJECTIVE: The aim of the present study was to verify whether drugs injected into the endolymphatic sac (ES) can reach the cochlea and possibly treat inner ear disorders.
STUDY DESIGN: Prospective cohort study.
SETTING: Tertiary referral center, Otolaryngology Department, University of Verona.
SUBJECTS AND METHODS: Patients with Ménière's disease (MD) who were candidates for ES decompression were selected. Nineteen subjects received dexamethasone (DEX) via injection into the ES. To objectively define whether substances administered into the ES could reach the cochlea, we added gadolinium (GD) in three patients. All subjects had intraoperative electrocorticogram recordings and an audiologic follow-up. The three subjects who underwent injection of the DEX-GD solution were followed-up with magnetic resonance imaging. The audiological data are presented during a follow-up period of 12 months.
RESULTS: Intraoperative electrocochleography recordings revealed no changes in two patients and summating potentials and compound action potential latency and wave-form modifications in all the other subjects. GD distribution was observed from 48 hours to one week after ES injection into the cochlea of the three subjects injected with DEX-GD. GD-related enhancement of inner ear structures lasted more than two weeks in all subjects. Pure tone average results showed hearing improvement of at least 20 dB HL in 42 percent of patients (8 of 19) at the 12-month follow-up. Statistically significant differences emerged between the mean pure tone average of the ES procedure subjects at one and 12 months after surgery ($P = 0.0096$).
CONCLUSION: This novel approach might reveal new prospects for treating viral, metabolic, autoimmune, and genetic disorders of the cochlea.

Emerging therapies such as stem cells, gene therapy, and neurotrophic factors may open up new prospects for the treatment of inner ear disorders. In particular, patients with sudden hearing loss, immunomediated disorders, and Ménière's disease (MD) could benefit from these new therapies. Most of these diseases constitute a major challenge for ENT doctors because there is no definitive and effective treatment.[1,2] Today for MD, only vertigo spells can be treated effectively with ablative procedures, whereas hearing loss and tinnitus remain unsolved problems. The blood−labyrinthine barrier acts similarly to the blood−brain barrier by limiting the diffusion of systemic drugs to the inner ear.[3] At the present time, two local procedures[4] are being studied to administer drugs into the inner ear compartments in humans: 1) intratympanic (IT) delivery, which involves depositing the therapeutic agent in the middle ear; and 2) intracochlear delivery, which depends on injection either through the round window membrane or via a cochleostomy. The perilymphatic compartment is the target of these two methodologies, but only the IT route has been widely adopted to deliver steroids to the human cochlea. The results of such therapy are often unpredictable,[1] and part of this substantial variability of results, ranging from complete recovery to no improvement, may be attributable to inadequate distribution into the endolymphatic compartments (ECs). To the best of our knowledge, none of the previously described methodologies have yielded either radiologic or electrophysiologic evidence of distribution into the human ECs. Promising results with stem cells[5,6] and mostly gene therapy administered via the scala media in animal models[7-9] could be the basis for developing new effective strategies for treating inner ear disorders.

Among hearing preservation procedures in MD, endolymphatic sac (ES) surgery has been considered a safe procedure, and in our opinion the ES might represent an appropriate entrance route to the endolymphatic space of the scala media (ESp-SM). Animal models have shown that ES

injections of viral vectors can successfully reach the ESp-SM,[10] and cochlear hair cell regeneration has been achieved after endolymphatic injections of Math1 gene via the ESp-SM.[7,8]

In humans, the therapeutic potential of steroid instillation into the ES in MD has been explored by Kitahara et al,[11] who discovered good outcomes in terms of controlling spells of vertigo and hearing function. However, these authors combined the procedure with drainage of the sac, thereby biasing the individual effect of each procedure.

The aim of the present study was to objectively verify with imaging or intraoperative electrophysiology whether substances injected into the ES can indeed reach the cochlea. Nineteen patients with MD undergoing ES decompression participated at the study: three patients received an injection of dexamethasone (DEX) in addition to gadolinium (GD) into the ES, and 16 received DEX alone. To monitor the possible hydrodynamic effects of modifying endolymphatic pressure and volume[12-14] with the injection of fluid (DEX plus GD or GD alone) into the ES, all patients had intraoperative electrocochleography (ECoG) recordings. An audiologic and neuro-otologic follow-up was conducted to investigate the safety and effectiveness of the ES procedure. In addition, the three patients receiving DEX plus GD underwent serial magnetic resonance imaging (MRI) studies. Here, the findings, potential, and limitations of this novel procedure are discussed.

Materials and Methods

The present study is a prospective cohort study on patient-based clinical population recruited during the period from January 2008 to January 2009. The study was conducted at the Department of Otolaryngology (tertiary referral center) of the University of Verona (Verona, Italy). All participants were affected by definite MD, according to the criteria of the American Academy of Otolaryngology-Head and Neck Surgery;[15] they had also received medical therapy (diuretics, betahistine, low-salt diet) for at least six months. All participants performed a complete audiologic evaluation with pure tone audiometry (PTA), speech audiometry, impedance audiometry, auditory brainstem-evoked potentials, ECoG, and electrical promontory stimulation with IT electrodes and the Tinnitus Handicap Inventory (THI). They also underwent a neuro-otologic evaluation that included an eye-movement bedside examination, caloric test, and vestibular-evoked myogenic potentials (VEMPs).

Nineteen patients met the inclusion criteria and were submitted to ES decompression. Sixteen patients underwent ES decompression with injection of DEX alone. Three patients accepted the procedure with local administration of a DEX-GD solution. Patients underwent classic ES decompression and received 27-gauge spinal needle injections into the ES with 0.2 mL of DEX alone (dexamethasone sodium phosphate 4 mg/1 mL; Mayne Generics) or DEX plus 20 percent gadobutrol (10-[(1SR,2RS)-2,3-dihydroxy-1-hydroxy-methylpropyl]-1,4,7,10-tetraazacyclo-dodecane-
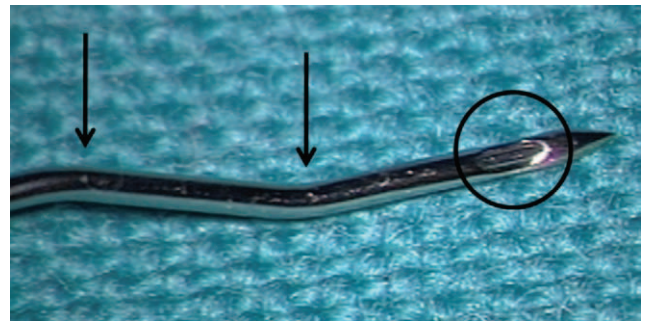
Figure 1 Needle preparation. The 27-gauge Whitacre (*circle*) spinal needle is modified to make it suitable for reaching the ES: two curvatures are produced (*arrows*).

1,4,7-triacetic acid, gadolinium-complex; Gadovist, Schering SpA).

The 27-gauge Whitacre spinal needle was modified to make it suitable for reaching the ES correctly (Fig 1). ES injections into the ES were performed with 0.2 mL of solution at a flow rate of approximately 0.1 mL/s. The injections were done by hand with a 1-mL insulin syringe, and its rate was only approximately measured. Complete surgical exposure of the ES up to the ED was obtained (Fig 2) to inject the solution into the lumen of the ES and visualize its dilatation as a result of the injection.

Intraoperative ECoG potentials (summating potentials [SPs] and compound action potentials [CAPs]) were recorded from electrodes placed on the round window with a reference on the ipsilateral tragus during pressure and volumetric changes of inner ear structures caused by the administration of the solution. A 10-channel evoked potential system (Medelec Synergy N-EP, VIASYS Healthcare, San Diego, CA) was used with a filter setting of 3 Hz to 3 KHz and a 2.5-mV amplifier. The recorded potentials were stored and analyzed offline.

Postoperative 1.5-T MRI follow-up evaluations were performed for the first week and weekly for the subsequent three weeks in patients who underwent ES administration of the DEX-GD solution. Inner ear structures were studied with three-dimensional Fourier transformation-constructive interference in the steady state (FT-CISS), spin echo T1-weighted sequences.

The 1.5-T MRI scans were performed by the use of a 1.5-T Magnetom Symphony Maestro Class device (Syngo MR 2002B model; Siemens, Erlangen, Germany) and a CP Head Array Coil (Siemens). A coronal T2-weighted sequence (TR 4850, TE 108, thickness 4 mm) was acquired as a scout view. The following scan was a gradient echo three-dimensional T1-weighted image (144 slices, flip angle 12°, thickness 1 mm, matrix 256 × 256 interpolation) to have a general view of the brain. Inner ear structures were studied in the axial plane with two sequences: three-dimensional 3D FT-CISS (28 slices, TR 13.88, TE 6.94, thickness 0.70 mm, flip angle 70°, matrix 320 × 320 interpolation), including maximum intensity projection volumetric reconstructions, and spin echo T1-weighted
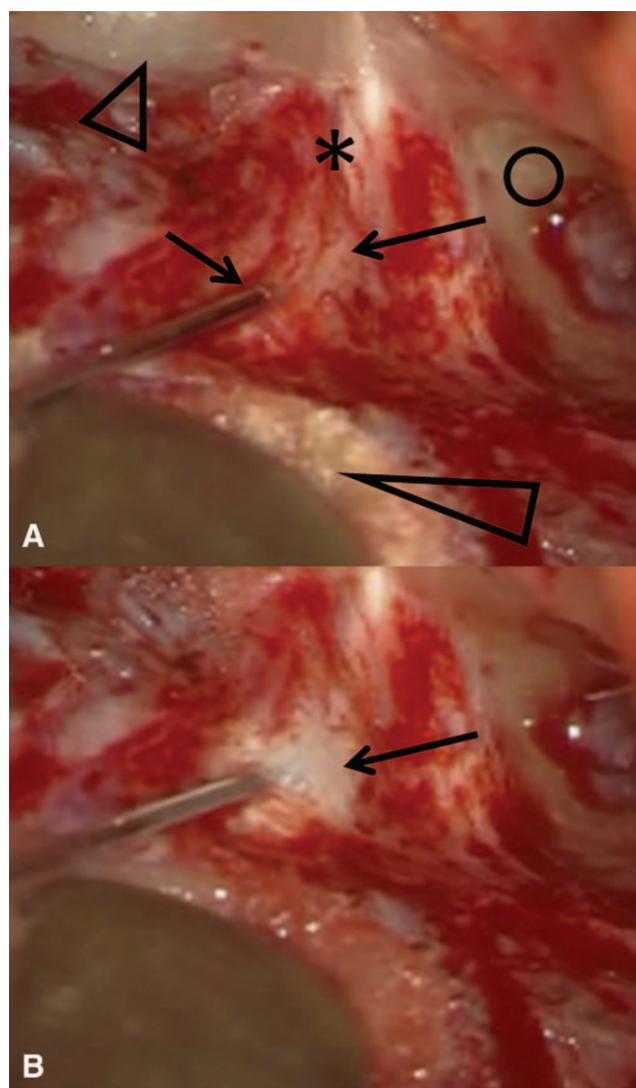
Figure 2   Surgical view of the exposed ES (right ear). (**A**) Mastoidectomy with exposure of the posterior semicircular canal (*short arrowhead*), sigmoid sinus gently depressed with the sigmoid sinus retractor (*long arrowhead*), retrofacial area (*circle*), ES (*long arrow*), and ED (*asterisk*). The spinal needle (*short arrow*) is inserted into the ES. (**B**) The injection produced distinct dilatation of the ES (*arrow*).

images (12 slices, TR 578, TE 17, thickness 2.5 mm, fat suppression, matrix 256 × 256). Three-dimensional FT-CISS images were obtained to furnish a correct anatomical view of the cerebellopontine angle and of the labyrinthine fluid spaces. An axial spin echo sequence was performed to highlight the presence of the paramagnetic contrast agent and to identify its position.

Clinical, audiologic, and neuro-otologic follow-up evaluations were performed at one, three, six, and 12 months. Significant hearing improvement or deterioration was considered when the PTA presented changes of at least 20 dB HL. Differences between groups were tested by the use of *t* test and nonparametric test (Mann–Whitney *U* test/χ^2 test; two-tailed) as appropriate.

All patients were informed as to the experimental procedures and signed a consent form. The procedures were approved by the Ethics Committee of the University of Verona School of Medicine.

Results

All patients but one completed the 12-month follow-up. This patient complained of incapacitating vertigo spells during follow-up (2 months after surgery) and subsequently underwent vestibular neurectomy to control the symptoms effectively. Intraoperative ECoG recordings were performed in all patients. In two patients, no changes could be observed with intraoperative ECoG after ES injection. One is the patient that, after obtaining no benefit from endolymphatic surgery, underwent vestibular neurectomy; the other patient had severe cochlear otosclerosis and had no changes in tinnitus and hearing threshold after sac surgery. In all the other subjects, changes in the wave-form or an increase in latency (mean, 0.24 ms; range, 0.16-0.39 ms) two to 10 minutes after the injection could be observed. Wave-form changes consisted mainly in modifications of SPs (9 subjects) and/or CAP amplitude variations (12 patients). Only one patient experienced an isolated increase in latency, whereas all other subjects showed associated latency and wave-form changes (Fig 3). All these changes reverted to normal within 20 to 60 minutes after the injection.

Distribution of GD was observed after a few hours in the ES area of the three subjects. A few hours after injection, it was not always easy to differentiate GD enhancement from blood in the area of the ES (Fig 4). All subjects showed initial distribution of GD from the ES to the vestibule and semicircular canals and subsequently to the basal, middle,
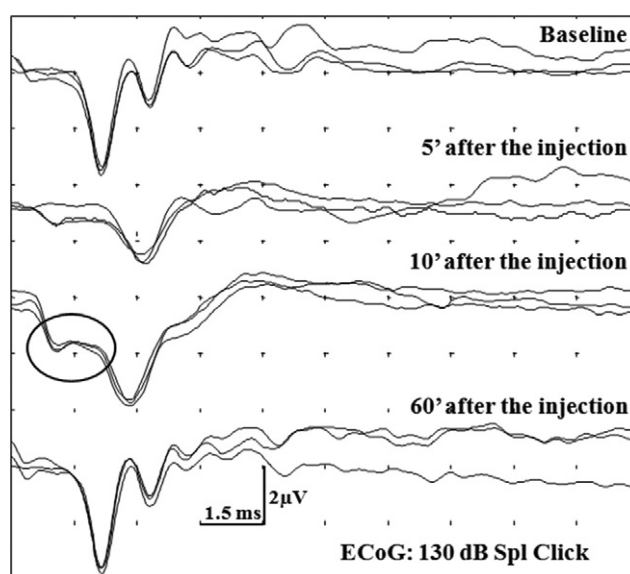
Figure 3   Intraoperative ECoG recordings during ES DEX administration. Increased latency and change in CAPs morphology with appearance of SPs (*circle*) are evident five to 10 minutes after injection.
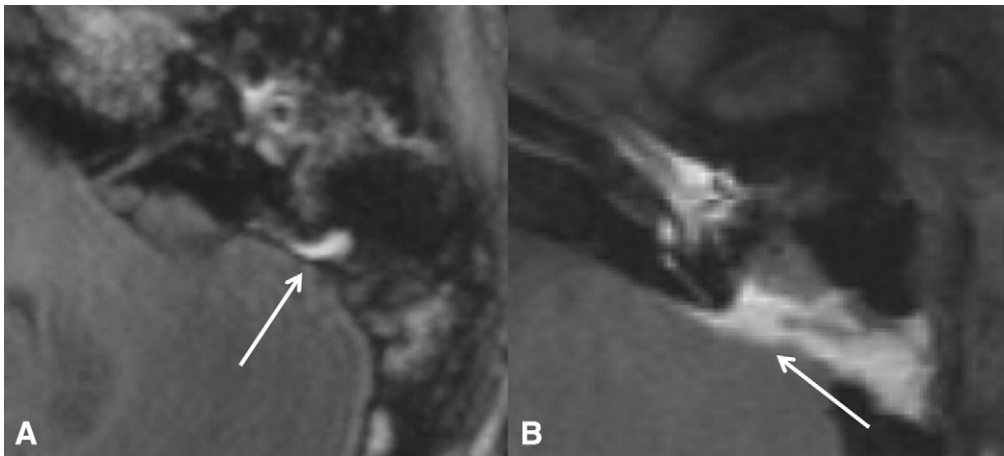
Figure 4   MRI T1-weighted spin echo, axial view images of ES GD-DEX administration (2 subjects: left ears). (**A**) Four hours after ES administration: high GD signal in the ES (*arrow*). (**B**) Six hours after ES administration: high GD signal in the surgical field and ES area (*arrow*).

and apical turns of the cochlea (Fig 5). Enhancement of the ES area was observed within four hours of the procedure. After approximately 24 hours, distribution of the GD was observed in the vestibule and semicircular canals in all subjects.

After 48 hours, GD diffusion was observed in the cochlear basal turn of two patients. In these two patients, all cochlear turns appeared clearly enhanced at 96 hours, whereas the other patient showed only faint enhancement of the basal turn. At the one-week examination, high gadolinium signal up to the apical turn was observed in all subjects.

Reliable enhancement of the ECs of the patients was observed two weeks or more after injection (mean, 16.3 days; range, 14-21 days). No GD-related contrast enhancement of cerebrospinal fluid was observed during the MRI follow-up, and no side effects were observed in any of the participants.

Table 1 summarizes the mean results of the PTA, THI, caloric test, and VEMPs at baseline and at one, three, six, and 12 months' follow-up. PTA results showed significant hearing improvement in 42 percent of patients (8 of 19) at the 12-month follow-up examination. The mean PTA at baseline and at the 12-month test was 48.04 ± 12.54 dB HL and 33.42 ± 18.74 dB HL, respectively. Statistically significant differences emerged between the baseline mean PTA and the 12-month control ($P = 0.0096$). Four patients
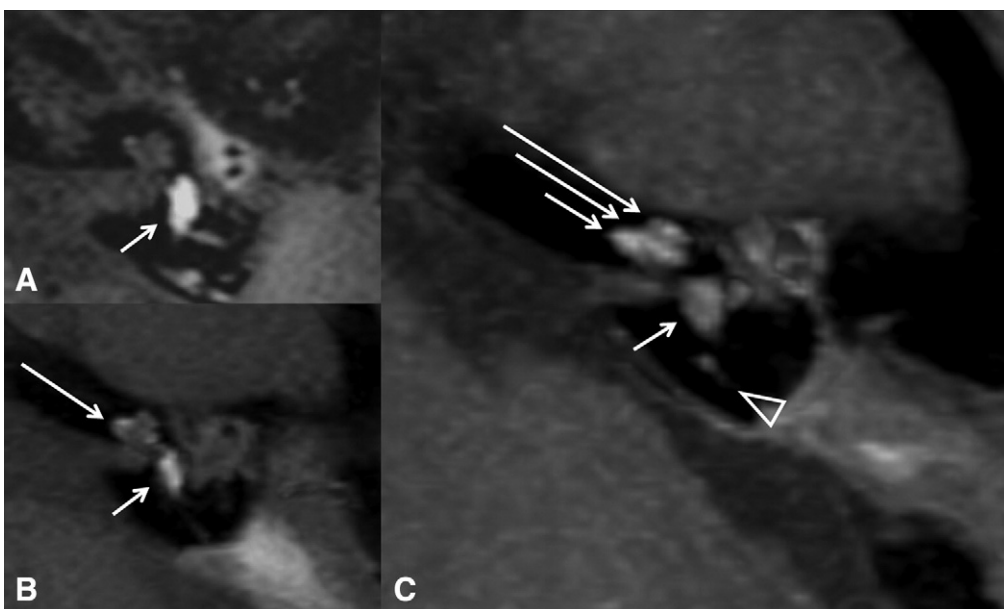
Figure 5   MRI T1-weighted spin echo, axial view images of ES GD-DEX administration (left ear). (**A**) At 24 hours after ES administration: high GD signal in the vestibule (*short arrow*). (**B**) At 48 hours after ES administration: GD-related enhancement in the vestibule (*short arrow*) and cochlear basal turn (*long arrow*). (**C**) At 96 hours after ES administration: high GD signal in the vestibule (*short arrow*), posterior semicircular canal (*arrowhead*), and all the cochlear turns (*3 arrows*).

Table 1
Audiologic and neuro-otologic results of the population

ES injection patients	Audiologic and neuro-otologic follow-up				
	Baseline	1 month	3 months	6 months	12 months
PTA, dB HL, mean ± SD	48.04 ± 12.54	51.02 ± 11.21	42.19 ± 19.36	36.68 ± 22.27	33.42 ± 18.74
Statistical analysis between follow-up times, baseline versus:		$P = 0.4451$	$P = 0.2777$	$P = 0.0628$	$P = 0.0096*$
THI, total score, mean ± SD	35.2 ± 19.3	21.6 ± 16.8	26.9 ± 17.4	22.7 ± 12.3	22.3 ± 14.1
Statistical analysis between follow-up times, baseline versus:		$P = 0.0285*$	$P = 0.1660$	$P = 0.0227*$	$P = 0.0253*$
Caloric weakness (caloric paresis/paralysis), %	84	94	89	89	89
VEMPs, absence, %	63	63	68	74	74

ES, endolymphatic sac; *PTA,* pure tone average; *THI,* Tinnitus Handicap Inventory; *VEMPs,* vestibular-evoked myogenic potentials.
*Statistically significant.

showed hearing deterioration at the 12-month follow-up. At the one-month follow-up, most of the patients experienced a significant ($P = 0.0285$) subjective reduction in tinnitus as documented by the THI total score (Table 1). This trend was confirmed as stable in subsequent examinations. No statistically significant differences emerged in the caloric test or in VEMPs at follow-up.

Discussion

Currently, the most widely adopted therapeutic procedure for treating acquired inner ear disorders is the IT administration of drugs. Steroid injections through the tympanic membrane are routinely performed for treating sudden hearing loss, immunomediated disorders, and MD. The radiological demonstration that perilymphatic and not endolymphatic diffusion of intratympanic GD may be observed in MD subjects[16,17] could account for the variability of the results of IT steroid therapy[1,18] and the absence of evidence-based conclusions that the treatment is effective. Other surgical approaches, such as direct round window administration[19] or the cochleostomy route, as used for cochlear implants,[4] may cause trauma, infection, and, in any case, may not offer the possibility of reaching the ESp-SM.[20]

To the best of our knowledge, the ES approach described here may be a possible route capable of providing distribution of substances into the human cochlea. The present study yielded both radiologic and electrophysiologic evidence that substances injected into the human ES can reach the cochlea, presumably the ESp-SM. At the 12-month audiologic and neuro-otologic follow-up, the ES injection procedure appeared safe for residual hearing and vestibular function.

The ES injection procedure with DEX-GD solution showed gradual GD diffusion from the ES and duct up to the apical turn of the cochlea in all subjects, which lasted more than two weeks in the inner ear. There was no evidence of cerebrospinal fluid enhancement at the MRI follow-up examination. This finding indicates that the injection was performed between the two layers of the ES into the endolymphatic space without damaging the deeper layer. Furthermore, the procedure of injecting the DEX-GD solution may be considered safe for residual hearing function because no patients showed any significant PTA deterioration.

Significant changes in SPs and CAPs were observed with dilatory injections in all but two patients who presented no changes in SPs and/or CAPs. One of these subjects had severe cochlear otosclerosis that could have prevented pressure and/or volume increases in the ESp-SM after injection. In all other patients, ES injection-related pressure and/or volume changes may have been rapidly (within 60-100 seconds) transmitted to the ESp-SM and returned to normal after 20 to 60 minutes. However, temporary modifications in the SP and CAPs could be also ascribed to temporary changes in the ionic composition of the endolymph or to minor and reversible traumatic effects. These findings clearly suggest that the ES procedure produces significant modifications of the ESp-SM as experimentally demonstrated by Salt et al.[12]

According to the ECoG findings, it may be assumed that the substances administered into the ES may be distributed through the ECs to ESp-SM, confirming the results of previous studies in the animal model.[8] The slow distribution and lengthy permanence of GD along the inner ear may be further proof of the distribution of GD into the ESp-SM because of the extremely low flow rate of endolymph in normal conditions and its relative isolation.

The audiologic examination showed a slightly greater percentage of patients with PTA threshold improvement as

compared with the findings of Kitahara et al[11] (42% vs 36.5%). Differences in the criteria adopted to define hearing improvement (10 dB HL vs 20 dB HL in the present study) and in follow-up time (7 years vs 12 months) emerged between these two studies. The results of ES injection of the steroid showed better outcomes, albeit only with a short follow-up period. These promising data seem to show an additional beneficial effect of steroid administration into the ECs and dilation of the ES as compared with ES decompression alone.

The ES injection procedure controlled spells of vertigo in 95 percent of patients. No cases of vestibular ablation related to the procedure were observed. Furthermore, no statistically significant differences emerged in the caloric test or in VEMPs at follow-up. These data are in agreement with the recent finding that acute endolymphatic hydrops has no effect on the vestibular system in the animal model.[21]

The main limitations of our study are the short follow-up, the absence of a randomized control group, and the resolution of the 1.5-T MRI that showed the cochlea as a single enhanced canal. The use of 3.0-T MRI would have made it possible to differentiate between perilymphatic and endolymphatic spaces. In addition, the observation that GD distributes from the ES to the ESp-SM does not necessarily predict the pharmacokinetics of other substances into the inner ear compartments.

Among the different drug-delivery methods for reaching the inner ear, the deposition of substances into the ES might afford an excellent drug access point that could be extended to gene[5,22] and stem cell[6] therapy. In particular, this new approach could be used to deliver substances to the inner ear with different strategies. "Single-shot therapy" via the ES route would be suitable for the treatment of sensorineural hearing loss and/or vestibular deficits with stem cells[5,6] and gene therapy.[7-9] The end point of single shot therapy should be the regeneration of cochlear and/or vestibular hair cells. The ES approach has the advantage of directly reaching the endolymphatic space, which is an ideal anatomical compartment for such therapies because of its peculiarities: small size and relative isolation.

Patients with sudden hearing loss, immunomediated inner ear disorders such as Cogan syndrome, and prevention of iatrogenic ototoxicity (radiotherapy, aminoglycosides, or cisplatin) could benefit from "prolonged therapy" with steroids and neurotrophic factors. Despite the protracted distribution of GD obtained in the cochlea, this type of ES administration must rely on the development of slow-release biodegradable polymers and nanoparticle delivery.[4] "Continuous therapy" may be possible when fully implantable devices (microcatheters or pumps with rechargeable reservoirs) have been developed for humans.

In conclusion, the ES injection procedure offers a great opportunity of reaching the cochlea and presumably the endolymphatic space safely. This novel route might constitute an advance in therapy for inner ear disorders. Reaching the ECs may be essential to achieve results worthy of note with local therapy. Recently developed therapies and conventional local treatments might benefit greatly from this procedure. Larger randomized controlled studies are necessary to verify the efficacy of each treatment proposed using this novel route.

Author Information

From the ENT Department (Drs. Mandalà, L. Colletti, Carner, and V. Colletti) and Institute of Radiology (Drs. Cerini, Barillari, and Mucelli), University of Verona, Verona, Italy.

Corresponding author: Vittorio Colletti, MD, ENT Department, University of Verona, Piazzale L.A. Scuro, 10, 37100 Verona, Italy.

E-mail address: vittoriocolletti@yahoo.com.

Author Contributions

Marco Mandalà, developed the study, collected data, wrote the article; **Liliana Colletti,** wrote and revised the article; **Marco Carner,** wrote the article; **Roberto Cerini,** developed the study, revised the article; **Marco Barillari,** developed the study, revised the article; **Roberto Pozzi Mucelli,** developed the study, revised the article; **Vittorio Colletti,** performed surgeries, developed the study, wrote the article.

Disclosures

Competing interests: None.

Sponsorships: None.

References

1. Hamid M, Trune D. Issues, indications, and controversies regarding intratympanic steroid perfusion. Curr Opin Otolaryngol Head Neck Surg 2008;16:434–40.
2. Sajjadi H, Paparella MM. Meniere's disease. Lancet 2008;372:406–14.
3. Juhn SK, Hunter BA, Odland RM. Blood−labyrinth barrier and fluid dynamics of the inner ear. Int Tinnitus J 2001;7:72–83.
4. Swan EE, Mescher MJ, Sewell WF, et al. Inner ear drug delivery for auditory applications. Adv Drug Deliv Rev 2008;60:1583–99.
5. Hildebrand MS, Newton SS, Gubbels SP, et al. Advances in molecular and cellular therapies for hearing loss. Mol Ther 2008;16:224–36.
6. Beisel K, Hansen L, Soukup G, et al. Regenerating cochlear hair cells: quo vadis stem cell. Cell Tissue Res 2008;333:373–9.
7. Izumikawa M, Minoda R, Kawamoto K, et al. Auditory hair cell replacement and hearing improvement by Atoh1 gene therapy in deaf mammals. Nat Med 2005;11:271–6.
8. Kawamoto K, Ishimoto S, Minoda R, et al. Math1 gene transfer generates new cochlear hair cells in mature guinea pigs in vivo. J Neurosci 2003;23:4395–400.
9. Praetorius M, Brough DE, Hsu C, et al. Adenoviral vectors for improved gene delivery to the inner ear. Hear Res 2009;248:31–8.
10. Yamasoba T, Yagi M, Roessler BJ, et al. Inner ear transgene expression after adenoviral vector inoculation in the endolymphatic sac. Hum Gene Ther 1999;10:769–74.
11. Kitahara T, Kubo T, Okumura S, et al. Effects of endolymphatic sac drainage with steroids for intractable Meniere's disease: a long-term

follow-up and randomized controlled study. Laryngoscope 2008;118: 854–61.

12. Salt AN, Brown DJ, Hartsock JJ, et al. Displacements of the organ of Corti by gel injections into the cochlear apex. Hear Res 2009;250:63–75.

13. Ikino CM, de Almeida ER. Summating potential-action potential waveform amplitude and width in the diagnosis of Menière's disease. Laryngoscope 2006;116:1766–9.

14. Ohashi T, Nishino H, Arai Y, et al. Clinical significance of the summating potential-action potential ratio and the action potential latency difference for condensation and rarefaction clicks in Meniere's disease. Ann Otol Rhinol Laryngol 2009;118:307–12.

15. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. American Academy of Otolaryngology−Head and Neck Foundation, Inc. Otolaryngol Head Neck Surg 1995;113:181–5.

16. Naganawa S, Satake H, Kawamura M, et al. Separate visualization of endolymphatic space, perilymphatic space and bone by a single pulse sequence; 3D-inversion recovery imaging utilizing real reconstruction after intratympanic Gd-DTPA administration at 3 Tesla. Eur Radiol 2008;18:920–4.

17. Nakashima T, Naganawa S, Sugiura M, et al. Visualization of endolymphatic hydrops in patients with Meniere's disease. Laryngoscope 2007;117:415–20.

18. Ahn JH, Yoo MH, Yoon TH, et al. Can intratympanic dexamethasone added to systemic steroids improve hearing outcome in patients with sudden deafness? Laryngoscope 2008;118:279–82.

19. Plontke SK, Lowenheim H, Mertens J, et al. Randomized, double blind, placebo controlled trial on the safety and efficacy of continuous intratympanic dexamethasone delivered via a round window catheter for severe to profound sudden idiopathic sensorineural hearing loss after failure of systemic therapy. Laryngoscope 2009;119:359–69.

20. Plontke SK, Siedow N, Wegener R, et al. Cochlear pharmacokinetics with local inner ear drug delivery using a three-dimensional finite-element computer model. Audiol Neurootol 2007;12:37–48.

21. Kingma CM, Wit HP. Acute endolymphatic hydrops has no direct effect on the vestibular evoked potential in the guinea pig. J Vestib Res 2009;19:27–32.

22. Collado MS, Burns JC, Hu Z, et al. Recent advances in hair cell regeneration research. Curr Opin Otolaryngol Head Neck Surg 2008; 16:465–71.