# A Comparison of Endolymphatic Shunt Surgery and Intratympanic Gentamicin for Meniere's Disease

Alec W. Gibson, BS 1 Joon Moon, MD, PhD 1; Justin S. Golub, MD, MS; Jay T. Rubinstein, MD, PhD

**Objective:** To report audiovestibular outcomes following endolymphatic shunt surgery (ELS) and intratympanic gentamicin injections (ITG) in patients with Meniere's disease (MD).

Study Design: Retrospective matched cohort study

**Methods:** Patients with MD refractory to medical management between 2004 and 2017 were reviewed: 44 patients underwent ELS and had outcomes available, while 27 patients underwent ITG and had outcomes available. Mean follow-up durations for the ELS and ITG groups were 39.1 and 43.3 months, respectively. Twenty-six patients from the ELS group and 24 patients from the ITG group were then included in a pretreatment hearing- and age-matched analysis. Main outcome measures were successful control of vertigo, pure-tone average (PTA; 0.5, 1, 2 and 4 kHz), word recognition score (WRS), and treatment complications.

**Results:** A matched analysis showed vertigo control rates of 73.1% in the ELS group and 66.8% in the ITG group, which were not significantly different (P = .760). The change in PTA following treatment was statistically similar between the ELS group (6.2 dB) and ITG group (4.6 dB) (P = .521), while the change in WRS for the ELS group (+3.9 %) was significantly more favorable than the ITG group (-13.6 %) (P = .046). Chronic post-treatment unsteadiness was reported in 25.0% of the ITG group and was not encountered in the ELS group (P = .009).

**Conclusion:** ELS provided successful vertigo control at least as well as ITG with a lower incidence of audiovestibular complications.

Key Words: Meniere's disease, endolymphatic shunt, intratympanic gentamicin, vertigo, hearing.

Level of Evidence: 4

Laryngoscope, 130:2455-2460, 2020

#### INTRODUCTION

The initial management of Meniere's disease (MD) consists of lifestyle and dietary changes, including a low-sodium diet and use of diuretics. Such interventions are effective in roughly 85% of patients. However, in patients with MD refractory to medical management, more invasive treatment strategies should be considered. The treatment of disabling vertigo in medically refractory MD remains a controversial challenge to clinicians.

Traditionally, a number of surgical options, such as endolymphatic shunt (ELS), vestibular nerve section, and labyrinthectomy, have been developed to reduce the symptoms of MD.<sup>2,3</sup> Labyrinthectomy or vestibular nerve

From the Department of Otolaryngology—Head and Neck Surgery (A.W.G., J.T.R.), University of Washington School of Medicine, Seattle, USA; Samsung Medical Center (I.J.M.), Sungkyunkwan University School of Medicine, Seoul, South Korea; and the Department of Otolaryngology—Head and Neck Surgery (J.S.G.), Columbia University Vagelos College of Physicians and Surgeons, New York, USA.

Additional supporting information may be found in the online version of this article.

Editor's Note: This Manuscript was accepted for publication on November 11, 2019.

Funding for this work was provided in part by NIH grants F30 DA043941 and R01 DC014002. The authors have no financial relationships or conflicts of interest to disclose.

Presented at the 54th Annual Spring Meeting of the American Neurotology Society at COSM, Austin, Texas, U.S.A., May 3, 2019.
Send correspondence to Jay T. Rubinstein, MD, PhD, Virginia

Send correspondence to Jay T. Rubinstein, MD, PhD, Virginia Merrill Bloedel Hearing Research Center, Box 357923, University of Washington, Seattle, WA, 98195. E-mail: rubinj@uw.edu

DOI: 10.1002/lary.28445

section can provide definitive management for episodic vertigo; however, the former procedure leads to complete hearing loss and both procedures result in permanent vestibular dysfunction with resulting imbalance that can be lifelong.<sup>2,4</sup> In contrast, ELS is non-destructive, has favorable surgical morbidity, and has minimal impact on hearing. Hence it is a logical surgical option in the presence of functional hearing; however, controversies regarding its efficacy continue to exist and demonstrate the need for additional data.<sup>5–8</sup>

Intratympanic gentamicin injection (ITG) has been widely used in order to avoid the morbidity of surgical procedures. Gentamicin is employed to ablate, fully or partly, the vestibular function in the affected ear, and seems to be an effective treatment for vertigo complaints in MD.<sup>9</sup> Two randomized controlled trials have shown a beneficial effect of ITG for MD compared with placebo, and subsequent studies have further validated the effectiveness of ITG.<sup>10–14</sup> Despite its efficacy and less invasive nature (when compared with surgical procedures), ITG can be hazardous to hearing and can have significant long-term vestibular sequelae. While vestibular hair cells are more sensitive to gentamicin than cochlear hair cells, ITG can still lead to cochlear hair cell and spiral ganglion neuron injury.<sup>14–16</sup>

The first study directly comparing outcomes between ELS and ITG for intractable MD reported that ITG had better posttreatment functional outcomes as well as better overall quality of life scores but no statistically significant difference in vertigo control.<sup>17</sup> This provides further support for the comparability of both treatments with

regards to vertigo outcomes. The aim of the present study was to compare vestibular and auditory outcomes between ELS and ITG in patients with definite MD refractory to medical management.

#### MATERIALS AND METHODS

A retrospective chart review was conducted on patients with American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) definite unilateral MD who failed medical management and underwent ELS or ITG between 2004 and 2017. The initial medical management included low-salt diet, diuretics, and vestibular suppressants. If a patient had persistent vertigo attacks after conservative medical management for 3 to 6 months, ELS or ITG were offered. Which treatment was performed depended on which clinician the patient saw. One clinician performed only ELS, and two other clinicians performed only ITG. There were no known criteria that determined which patients saw which clinician.

All patients underwent pretreatment evaluation, including complete neurotological examination and audiological testing (pure-tone audiometry and word recognition score testing). Symptoms, such as frequency of major vertiginous episodes, chronic unsteadiness, and any other associated symptoms were noted. Treatment outcomes were evaluated at the last follow-up visit based on the 1995 guidelines of the AAO-HNS. 18 Frequency of major vertiginous episodes was measured, and successful control of vertigo was considered as Class A or B (reduced by 60% to 100%). If general imbalance/unsteadiness was newly developed after ELS or ITG and the symptom continued more than 6 months after the treatment through the last follow-up, then the patient was considered to have chronic unsteadiness. Puretone average (PTA; 0.5, 1, 2, and 4 kHz) and word recognition score (WRS) that were obtained before and 6 months after treatment were compared. Clinically significant hearing change was defined as a PTA change of ≥10 dB or a WRS change of >15%.

#### **Patient Characteristics**

The patient characteristics are summarized in Table I. A total of 47 patients were treated by ELS, with outcomes available for 44 patients. One patient had previously undergone ITG, one had received an intratympanic corticosteroid injection, and all remaining 42 patients had been treated with medical

TABLE I. Patient Characteristics of ELS and ITG Groups.			
	ELS group (n = 44)	ITG group (n = 27)	Р
Sex	Male: 20	Male: 10	.622 <sup>†</sup>
Age (yr)	Female: 24 $48.6 \pm 14.6$	Female: 17 $60.7 \pm 16.5$	.004 <sup>‡</sup>
Symptom period prior to each treatment (yr)	$5.5 \pm 5.7$	$6.0 \pm 5.6$	.925 <sup>‡</sup>
Follow-up duration (mo)	$39.1\pm30.5$	$43.3 \pm 37.2$	.904 <sup>‡</sup>
Preoperative PTA (dB)	$45.5\pm18.8$	$60.2 \pm 15.0$	.002‡
Preoperative WRS (%)	$71.4\pm24.8^{\S}$	$42.3\pm31.9^{\P}$	<.001‡

ELS = endolymphatic shunt surgery; ITG = intratympanic gentamicin injection; PTA = pure-tone average (0.5, 1, 2, and 4 kHz); WRS = word recognition score.

management only. Postoperative audiologic data were available in all 44 patients with follow-up. A total of 33 patients were treated with ITG, with outcomes available for 27. Four patients had previously undergone other invasive treatments for vertigo (three cases of endolymphatic sac decompressions and one case of intratympanic steroid injection), while the remaining 23 patients had been treated with medical management only. Post-procedure audiologic data were available in 25 patients (two patients were followed up after ITG but the posttreatment audiograms were missing from the medical record).

#### Endolymphatic Sac Surgery

After complete mastoidectomy, the sigmoid sinus and posterior fossa dura were skeletonized. The horizontal and posterior semicircular canals were identified. The endolymphatic sac was identified as a thickened portion of the dura, usually deep and inferior to the posterior semicircular canal, anterior to the sigmoid sinus, and superior to the jugular bulb. The lateral aspect of the sac was incised and a silastic sheet was placed into the sac extending into the mastoid cavity. All patients were discharged on postoperative day 1. All surgeries were performed by the same surgeon at a tertiary neurotologic referral center.

## Intratympanic Gentamicin Injection

Thirty-three patients with MD refractory to medical management underwent ITG. Injections were performed on an outpatient basis. The patients were placed in a supine position with head extension and contralateral rotation. Approximately 0.3 to 0.4~mL of 30~mg/mL buffered solution (pH 6.4) of gentamicin was slowly injected filling the middle ear space using a small-gauge needle, or through a ventilation tube. Weekly follow-up examinations were performed including pure-tone audiogram. Symptoms of vertigo, dizziness, hearing loss, tinnitus, and aural fullness were recorded. A titration method was used, in which a single injection was given with repeat injections performed for persistent vertigo attacks. If a significant hearing deterioration occurred, vertigo attacks stopped, or the frequency of attacks remained constant after repeated injections, further gentamicin injection was discontinued. No treatment was given to patients with less than one vertigo attack per month. ITG was administered by two surgeons with similar protocols for treatment and evaluation.

# Statistical Analysis

Comparison between the ELS and ITG groups was performed using the Mann-Whitney U test and Fisher's exact test. A P value <0.05 was considered to be statistically significant. Mean values are reported  $\pm$  standard deviation (SD). All statistical analyses were performed using GraphPad Prism 7 software. This study was approved by the institutional review board of the University of Washington.

#### RESULTS

# Outcomes of ELS

In the ELS group, 72.7% of patients had subjective improvement in vertigo symptoms after treatment. The degree of vertigo control following ELS was as follows: class A in 22 (50.0%) patients, class B in 10 (22.7%) patients, class C in three patients (6.8%), and class D in nine (20.5%) patients. The mean ( $\pm$ SD) PTA and WRS

<sup>&</sup>lt;sup>†</sup>By Fisher's exact test.

<sup>‡</sup>By Mann-Whitney U test.

<sup>§</sup>n = 43 (Spanish speaker).

 $<sup>^{\</sup>P}$ n = 25 (WRS testing not available in two patients).

results after ELS changed from 45.5 dB ( $\pm 18.8$ ) to 51.8 dB ( $\pm 26.9$ ) (P=.424), and 71.4% ( $\pm 24.8$ ) to 71.1% ( $\pm 32.9$ ) (P=.367), respectively. Eighteen of the 44 patients (40.9%) experienced hearing deterioration (for scattergrams of hearing data see Supplemental Data 1). No patients suffered from chronic unsteadiness after ELS. Ten patients underwent secondary treatment, including vestibular nerve section (n = 4), labyrinthectomy (n = 3), revision ELS (n = 2), or vestibular implant (n = 1)<sup>20,21</sup> for definitive vertigo control. No surgery-related complications were identified except worsening of hearing.

#### **Outcomes of ITG**

The mean (±SD) number of gentamicin injections was 2.6 ( $\pm 1.8$ ) (range: 1–9), with a mean cumulative dose of 23.3 ( $\pm 16.4$ ) mg. In the ITG group, 63.0% of patients had subjective improvement in vertigo symptoms after treatment. The degree of vertigo control was as follows: class A in nine (33.3%) patients, class B in 8 (29.6%) patients, class C in one (3.7%) patient, and class D in nine (33.3%) patients. The mean ( $\pm$ SD) number of gentamicin injections for patients who achieved successful vertigo control was 2.6 ( $\pm 1.4$ ) (range: 1–6), with a mean cumulative dose of 23.3 ( $\pm 12.8$ ) mg. The mean ( $\pm SD$ ) PTA and WRS results changed from 60.2 dB (±15.0) to 65.7 dB  $(\pm 15.7)$  (P = .295), and 42.3% ( $\pm 31.9$ ) to 28.0% ( $\pm 27.4$ ) (P = .085), respectively. Thirteen of 25 patients (52.0%) experienced hearing deterioration (for scattergrams of hearing data see Supplemental Data 2). Chronic unsteadiness was newly developed in eight patients (29.6%). Four patients underwent secondary treatment due to persistent disabling vertigo attacks, including labyrinthectomy (n = 3) and vestibular nerve section (n = 1). Middle ear infection was noted in one patient after ITG and treated with antibiotics.

## Comparison Between the ELS and ITG Groups

Before treatment, the mean preoperative PTA and WRS in the ELS group were 45.5 dB and 71.4%, while those in the ITG group were 60.2 dB and 42.3%, respectively. The ITG group started with worse hearing in terms of both PTA (P = .002) and WRS (P = .0003) as compared with the ELS group. Vertigo control and hearing outcomes between the ELS and ITG groups are shown in Table II. Bilateral audiometric data is displayed in Supplemental Data 3 and demonstrates stable hearing before and after treatments in unaffected ears, with no differences between groups. In the ELS group, 72.7% of patients had subjective improvement in vertigo symptoms after treatment, while in the ITG group, 63.0% had a posttreatment subjective improvement of vertigo. There was no statistically significant difference in postoperative vertigo control between the two groups (P = .453). Of note, although it is generally not considered as a treatment failure, chronic unsteadiness occurred in 29.6% of patients who underwent ITG, while no patient reported this symptom after ELS. The difference in the development of chronic unsteadiness between the two groups was statistically significant (P < .001). The two groups did not show a significant difference in terms of

TABLE II.

Vertigo Control and Hearing Outcomes Between Endolymphatic Shunt and Intratympanic Gentamicin Injection Groups.

ELS group (n = 44)	ITG group (n = 27)	Р
72.7% (32/44)	63.0% (17/27)	.453 <sup>†</sup>
0% (0/44)	29.6% (8/27)	<.001 <sup>†</sup>
$\textbf{51.8} \pm \textbf{26.9}$	$65.7\pm15.7^{\S}$	.004 <sup>‡</sup>
$71.1\pm32.9^{\parallel}$	$28.0\pm27.4^{\P}$	<.001 <sup>‡</sup>
$\textbf{6.3} \pm \textbf{23.4}$	$5.5\pm9.0^{\S}$	.356 <sup>‡</sup>
$-0.2\pm29.2^{\parallel}$	$-14.4\pm27.8^{\P}$	.049 <sup>‡</sup>
40.9% (18/44)	52.0% (13/25) <sup>§</sup>	.453 <sup>†</sup>
	$\begin{array}{c} \text{(n = 44)} \\ \\ 72.7\% \ (32/44) \\ \\ 0\% \ (0/44) \\ \\ 51.8 \pm 26.9 \\ \\ 71.1 \pm 32.9^{\parallel} \\ \\ 6.3 \pm 23.4 \\ \\ -0.2 \pm 29.2^{\parallel} \end{array}$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$

ELS = endolymphatic shunt surgery; ITG = intratympanic gentamicin injection; PTA = pure-tone average (0.5, 1, 2, and 4 kHz); WRS = word recognition score.

changes in PTA (pre- and posttreatment PTA difference) (P=.356). However, the change in WRS was significantly more favorable for the ELS group than the ITG group (P=.049).

Due to the differences in age and preoperative hearing between the two groups, there could be a bias in interpreting the hearing and vertigo outcomes between the two groups. Therefore, we restricted both groups in order to match age and hearing levels by removing patients whose age is under 30 years (n = 4), whose PTA is under 30 dB

TABLE III.

Vertigo Control and Hearing Outcomes Based on a Matched
Analysis.

	ELS group (n = 26)	ITG group (n = 24)	P
Sex	Male: 14	Male: 9	.272 <sup>†</sup>
Age (yr)	Female: 12 53.7 $\pm$ 11.2	Female: 15 57.3 $\pm$ 13.9	.244 <sup>‡</sup>
Symptom period prior to each treatment (yr)	$6.6 \pm 6.9$	$\textbf{5.8} \pm \textbf{5.9}$	.491 <sup>‡</sup>
Follow-up duration (months)	$40.9 \pm 32.5$	$43.9 \pm 36.8$	.882 <sup>‡</sup>
Preoperative PTA (dB)	$\textbf{56.4} \pm \textbf{12.2}$	$60.2\pm15.3$	.273 <sup>‡</sup>
Preoperative WRS (%)	$\textbf{56.3} \pm \textbf{21.8}$	$\textbf{42.8} \pm \textbf{32.6}$	.120 <sup>‡</sup>
Vertigo control rate	73.1% (19/26)	66.8% (16/24)	.760 <sup>†</sup>
Chronic unsteadiness	0	25.0% (6/24)	.009 <sup>†</sup>
Postoperative PTA (dB)	$\textbf{62.5} \pm \textbf{26.3}$	$64.7 \pm 15.2$	.352 <sup>‡</sup>
Postoperative WRS (%)	$60.2 \pm 36.1$	$\textbf{29.8} \pm \textbf{26.4}$	.002 <sup>‡</sup>
Change in PTA (dB)	$\textbf{6.2} \pm \textbf{27.0}$	$4.6 \pm 7.9$	.521 <sup>‡</sup>
Change in WRS (%)	$\textbf{3.9} \pm \textbf{35.5}$	$-13.6\pm28.1$	.046 <sup>‡</sup>
Worsening of hearing (% of patients)	38.5% (10/26)	50.0% (12/24)	.569 <sup>†</sup>

ELS = endolymphatic shunt surgery; ITG = intratympanic gentamicin injection; PTA = pure-tone average (0.5, 1, 2, and 4 kHz); WRS = word recognition score.

<sup>†</sup>By Fisher's exact test.

<sup>&</sup>lt;sup>‡</sup>By Mann-Whitney *U* test.

<sup>§</sup>n = 25 (post-procedure audiometry unavailable in two patients).

<sup>&</sup>lt;sup>¶</sup>n = 24 (post-procedure WRS testing unavailable in three patients).

n = 43 (Spanish speaker).

<sup>†</sup>By Fisher's exact test.

<sup>&</sup>lt;sup>‡</sup>By Mann-Whitney *U* test.

TABLE IV.
Association of Age with Vertigo and Hearing Outcomes.

	Patients aged 10–52 years (n = 34)	Patients aged 53–98 years (n = 37)	Р
Mean age (yr)	$40.2\pm10.5$	$65.1\pm10.5$	<.001 <sup>‡</sup>
Vertigo control rate	70.6% (24/34)	67.6% (25/37)	.803 <sup>†</sup>
Change in PTA (dB)	$\textbf{5.4} \pm \textbf{20.0}$	$6.6\pm19.0^{\S}$	.585 <sup>‡</sup>
Change in WRS (%)	$-5.3\pm27.9^{\P}$	$-5.3\pm30.9^{\S}$	.849 <sup>‡</sup>
Worsening of hearing (% of patients)	44.1% (15/34)	45.7% (16/35) <sup>§</sup>	>.999†

ELS = endolymphatic shunt surgery; ITG = intratympanic gentamicin injection; PTA = pure-tone average (0.5, 1, 2, and 4 kHz); WRS = word recognition score.

(n = 9), or whose WRS is over 90% (n = 5) in the ELS group, and by removing patients whose age is 80 years or older (n = 3) in the ITG group. After this restriction, a matched analysis was possible, and the results are displayed in Table III. Vertigo control rates for the ELS and ITG groups were 73.1% and 66.8%, respectively, and did not significantly differ (P = .760). The change in PTA following treatment was similar between the ELS group and ITG group (P = .521), while the change in WRS for the ELS group was significantly more favorable than the ITG group (P = .046). Chronic post-treatment unsteadiness occurred in 25.0% of the ITG group and was not encountered in the ELS group (P = .009).

To further examine whether age or preoperative hearing could serve as confounders that introduce bias, we performed several additional analyses to determine the effect of age and pre-operative hearing on vertigo and hearing outcomes. We first divided all 71 patients into two groups based on age (patients whose age was between 10 and 52 years, and patients whose age was between 53 and 98 years) and analyzed differences in

TABLE V.
Association of Pretreatment PTA with Vertigo and Hearing Outcomes.

	Patients with pretreatment PTA < 55 (n = 34)	Patients with pretreatment PTA > 55 (n = 35)	P
Mean Preoperative PTA (dB)	35.7 ± 13.4	$65.5 \pm 9.0$	<.001‡
Vertigo control rate	70.6% (24/34)	68.6% (24/35)	>.999†
Change in PTA (dB)	$\textbf{10.48} \pm \textbf{20.6}$	$\textbf{1.6} \pm \textbf{17.3}$	.050 <sup>‡</sup>
Change in WRS (%)	$-7.0\pm26.9^{\S}$	$-3.7\pm31.6$	.820 <sup>‡</sup>
Worsening of hearing (% of patients)	44.1% (15/34)	45.7% (16/35)	>.999†

ELS = endolymphatic shunt surgery; ITG = intratympanic gentamicin injection; PTA = pure-tone average (0.5, 1, 2, and 4 kHz); WRS = word recognition score.

TABLE VI.
Association of Pretreatment WRS with Vertigo and Hearing
Outcomes.

	Patients with pretreatment WRS > 70 (n = 35)	Patients with pretreatment WRS < 70 (n = 32)	P
Mean Preoperative WRS (%)	$86.4 \pm 9.8$	$33.1 \pm 19.2$	<.001 <sup>‡</sup>
Vertigo control rate	71.4% (25/35)	68.8% (22/32)	>.999†
Change in PTA (dB)	$6.4\pm18.6$	$\textbf{5.0} \pm \textbf{20.9}$	.642 <sup>‡</sup>
Change in WRS (%)	$-12.4\pm27.5$	$\textbf{2.5} \pm \textbf{29.6}$	.139 <sup>‡</sup>
Worsening of hearing (% of patients)	45.7% (16/35)	43.8% (14/32)	>.999†

ELS = endolymphatic shunt surgery; ITG = intratympanic gentamicin injection; PTA = pure-tone average (0.5, 1, 2, and 4 kHz); WRS = word recognition score.

vertigo control rate, mean change in PTA, and mean change in WRS. The results of this analysis are displayed in Table IV. We performed similar analyses by dividing patients based on their preoperative PTA (patients whose PTA was less than 55 vs greater than 55) and preoperative WRS (patients whose WRS was greater than 70 vs less than 70). The results of these analyses are outlined in Tables V and VI. Overall, there were no significant differences in vertigo control, mean change in PTA, or mean change in WRS based on age or preoperative hearing.

#### DISCUSSION

The management of disabling vertigo in patients with medically refractory MD remains controversial. ITG has emerged as a popular procedure for treating disabling vertigo in MD, and surgical procedures are generally less widely performed due to the perception that ITG is less invasive than surgery. However, ITG is a destructive procedure and directly comparing the outcomes of ELS and ITG is necessary for patient counseling as well as selecting an appropriate procedure for the treatment of MD.

In this study, hearing was stable or improved in 59.1%, and successful vertigo control was achieved in 72.7% after ELS. This outcome is in accordance with previously reported results. Derebery et al.<sup>22</sup> reviewed the ELS literature and reported that hearing was improved or stable in 66% of patients, and vertigo was successfully controlled (class A or B) in 77% of patients. These results are quite successful, but skepticism remains due to lingering concerns raised by the "sham study" despite a thoughtful re-analysis of those data. Furthermore, a recent Cochrane review indicated insufficient evidence for the beneficial effect of endolymphatic sac surgery. 23 Additional well-designed randomized controlled studies would be necessary to definitively assess the relative efficacy of ITG and ELS. Ethical concerns, however, preclude a fully double-blinded study.

The ITG group showed a successful vertigo control rate of 63.0%, which is lower but statistically similar to the ELS outcome. A meta-analysis of ITG was performed

<sup>&</sup>lt;sup>†</sup>Bv Fisher's exact test.

<sup>&</sup>lt;sup>‡</sup>By Mann-Whitney *U* test.

<sup>§</sup>n = 35 (post-procedure audiometry unavailable in two patients).

<sup>&</sup>lt;sup>¶</sup>n = 32 (post-procedure WRS testing unavailable in two patients).

<sup>&</sup>lt;sup>†</sup>By Fisher's exact test.

<sup>&</sup>lt;sup>‡</sup>By Mann-Whitney *U* test.

<sup>§</sup>n = 32 (post-procedure audiometry unavailable in two patients).

<sup>†</sup>By Fisher's exact test.

<sup>&</sup>lt;sup>‡</sup>By Mann-Whitney *U* test.

by Cohen-Kerem et al.<sup>24</sup> and found an overall vertigo control rate of 93% (class A and B), but there was a large variability in vertigo outcome among studies. The cause of variability in outcome following ITG is unclear, but it may be related to the natural history of the disease, dosing differences, maternally inherited susceptibility to aminoglycoside ototoxicity, geographic differences, or ethnic population differences among studies.<sup>22,25</sup> In addition, the authors reported that average worsening of hearing was 1.5 dB after ITG.

Chia et al.<sup>26</sup> conducted a similar meta-analysis of ITG studies but with very different results, reporting a hearing loss rate of 25.1% across all studies. Derebery et al.<sup>22</sup> report a similar hearing loss rate of 25% in patients who received ITG. However, both hearing and vertigo outcomes after ITG can vary depending on the dose, titration, number, and frequency of injections, which has contributed to the large variability in outcomes of previous ITG studies.<sup>14,26,27</sup> In our study, 52.0% of patients showed hearing deterioration after ITG, which is higher than previous findings and could be the result of variability in the numbers of injections patients received along with other previously mentioned factors.<sup>14,22,25–27</sup>

Of note, in our study, eight out of 27 patients (29.6%) who underwent ITG developed chronic imbalance and unsteadiness after the treatment. Previous studies have also revealed that a significant portion of patients complained of chronic unsteadiness or postural instability after ITG. <sup>28,29</sup> Boleas-Aguirre et al. <sup>28</sup> reported that 15.5% of patients with MD treated with ITG showed unsteadiness, even though 81% of them achieved successful vertigo control. Unsteadiness after ITG has been frequently overlooked, but it should be taken into consideration when choosing an appropriate treatment and should be included in the informed consent process. Patients with chronic unsteadiness should be encouraged to get involved in a vestibular rehabilitation program, as this improved subjective evaluation of postural control in a previous study.<sup>29</sup> In severe cases, labyrinthectomy should be considered. While it is common for patients who undergo destructive procedures such as labyrinthectomies to have initial imbalance, this typically resolves and none of the ELS patients who underwent secondary procedures experienced chronic unsteadiness as a result. Of note, six patients with chronic unsteadiness after ITG underwent rehabilitation and continued to have persistent imbalance despite this intervention.

Elderly patients with MD showed a higher incidence of drop attacks and chronic unsteadiness. <sup>30,31</sup> In addition, Sunde et al. <sup>31</sup> reported that patients older than 65 years were more likely to have chronic unsteadiness after ITG and they therefore recommended alternative treatment options in this age group. In our study, four patients were older than 65 years among the eight patients who experienced chronic unsteadiness.

Comprehensive vestibular testing can provide additional objective data for evaluating vestibular function. At our institution, with a diagnosis of definite unilateral Meniere's disease, these tests are typically performed only prior to a destructive procedure to ensure the unaffected ear is healthy. Posttreatment vestibular testing

was not routinely performed for patients in this study but should be considered for future analyses. While the results of vestibular testing could also be important for the management of patients with chronic unsteadiness, the subsequent evaluation and management of these patients is beyond the scope of this study.

The use of intratympanic corticosteroid injections has recently emerged as an alternative to ITG.<sup>32</sup> An initial randomized control trial showed that intratympanic dexamethasone (ITD) results in significantly greater vertigo control compared to placebo.<sup>33</sup> A subsequent randomized control trial comparing ITD to ITG demonstrated that ITD is less effective at controlling vertigo than ITG,34 while a more recent randomized, double-blind control trial comparing intratympanic methylprednisolone to ITG showed similar outcomes between the two interventions.<sup>35</sup> While additional studies also support the effectiveness of intratympanic steroids in the treatment of MD, 32,36 others have shown a transient or lack of vertigo control following intratympanic steroids, and controversies remain regarding the efficacy of this treatment.  $^{32,37-39}$  To date, no studies comparing intratympanic steroid injections to ELS have been published. In our study, only one patient from each group received intratympanic steroids prior to ELS or ITG.

It is also important to note that there can often be significant symptom overlap between MD and vestibular migraine (VM), and rates of coexistence can be as high as 30-40% in certain cases. 40,41 Thus, VM should be considered when evaluating treatment outcomes for MD. We limited the patients in our study to those that met the AAO-HNS guidelines for definite MD in order to reduce the possibility of overlap with other vestibular conditions, since coexistence of VM and MD are significantly lower in cases of definite MD.<sup>41</sup> While none of the patients in the ELS and ITG groups had clinical characteristics that suggested VM, this does not completely rule it out in our cohorts. In addition, several studies have highlighted the potential role of allergy in MD. 42–45 The patients in our study were not evaluated for allergies; however, it remains a possible consideration in the treatment of MD.

In this study, the mean follow-up durations for the ELS and ITG groups were 39.1 and 43.3 months, respectively, which are longer than the minimum 2-year followup recommended by the 1995 AAO-HNS guidelines. Both groups also had similar mean disease durations prior to treatment (5.5 and 6.0 years, respectively). However, the mean age (60.7 years), preoperative PTA (60.2 dB), and preoperative WRS (42.3%) of the ITG group were significantly different than those of the ELS group (48.6 years, 44.5 dB, and 71.4%, respectively). These differences could affect vertigo and hearing outcomes and introduce bias. Therefore, we performed an additional analysis by restricting either group so that the two groups are age and hearing matched. This matched analysis still showed similar results: that vertigo control rate is comparable between the two groups while the ITG group may experience hearing deterioration and chronic unsteadiness after treatment. We performed additional analyses to determine the effect of age and preoperative hearing on outcome measures, which revealed no significant differences in vertigo control or change in hearing based on age or preoperative hearing. Furthermore, in a previous study, MD patients with mild-to-moderate hearing loss had a tendency toward decreased hearing over time, while those with severe-to-profound hearing loss generally did not experience further hearing deterioration. 46 The results of our analyses are consistent with these findings. Despite these additional analyses, the risk of measurement bias in our study remains present.<sup>47</sup> This could be reduced in future studies with the use of a standardized questionnaire for the evaluation of vertigo control, as described by Paradis et al. 17

#### CONCLUSION

ELS provided vertigo control at least as well as ITG with potentially better auditory outcomes and none of the chronic unsteadiness found in over 25% of the ITG group. This potential complication should be included in informed consent for ITG. While good results have been reported by some authors with ITG, ELS remains a valuable and extremely safe intervention after failure of medical management.

#### BIBLIOGRAPHY

- Sajjadi H, Paparella M. Meniere's disease. Lancet 2008;372:406-414.
- 2. Eisenman D, Speers R, Telian S. Labyrinthectomy versus vestibular neurectomy: long-term physiologic and clinical outcomes. Otol Neurotol 2001;22:539-548.
- 3. Hu A, Parnes L. 10-year review of endolymphatic sac surgery for intractable meniere disease. J Otolaryngol Head Neck Surg 2010;39:415–421.
  4. Langman A, Lindeman R. Surgical labyrinthectomy in the older patient.
- Otolaryngol Head Neck Surg 1998;118:739–742.

  Bretlau P, Thomsen J, Tos M, Johnsen NJ. Placebo effect in surgery for
- Meniere's disease: nine-year follow-up. Am J Otol 1989;10:259-261.
- 6. Thomsen J, Bonding P, Becker B, Stage J, Tos M. The non-specific effect of endolymphatic sac surgery in treatment of Meniere's disease: a prospective, randomized controlled study comparing "classic" endolymphatic sac surgery with the insertion of a ventilating tube in the tympanic mem-
- brane. Acta Otolaryngol 1998;118:769–773.

  7. Welling D, Nagaraja H. Endolymphatic mastoid shunt: a reevaluation of efficacy. Otolaryngol Head Neck Surg 2000;122:340-345.
- 8. Durland WF, Jr., Pyle GM, Connor NP. Endolymphatic sac decompression as a treatment for Meniere's disease. Laryngoscope
- 9. Pullens B, van Benthem P. Intratympanic gentamicin for Meniere's disease or syndrome. Cochrane Database Syst Rev 2011:CD008234. 10. Postema R, Kingma C, Wit H, Albers FW, Van Der Laan BF. Intratympanic
- gentamicin therapy for control of vertigo in unilateral Menire's disease: a prospective, double-blind, randomized, placebo-controlled trial. Acta Otolaryngol 2008;128:876–880.
- 11. Stokroos R, Kingma H. Selective vestibular ablation by intratympanic gentamicin in patients with unilateral active Meniere's disease: a prospective, double-blind, placebo-controlled, randomized clinical trial. Otolaryngol 2004;124:172-175.
- Quaglieri S, Gatti O, Rebechi E, Manfrin M. Intratympanic gentamicin treatment 'as needed' for Meniere's disease. Long-term analysis using the Kaplan-Meier method. Eur Arch Otorhinolaryngol 2014;271:1443-1449.
- 13. Rah Y, Han J, Park J, Choi B. Management of intractable Ménière's disease after intratympanic injection of gentamicin. Laryngoscope. 2015;125: 972–978.
- 14. Yetişer S. Intratympanic gentamicin for intractable Ménière's disease a review and analysis of audiovestibular impact. Int Arch Otorhinolaryngol 2018:22:190-194.
- 15. Jeong S, Kim L, Hur D, et al. Gentamicin-induced spiral ganglion cell death: apoptosis mediated by ROS and the JNK signaling pathway. Acta Otolaryngol 2010;130:670-678.
- 16. Kobayashi M, Sone M, Umemura M, et al. Comparisons of cochleotoxicity among three gentamicin compounds following intratympanic application. Acta Otolaryngol 2008;128:245–249.
- 17. Paradis J, Hu A, Parnes L. Endolymphatic sac surgery versus intratympanic gentamicin for the treatment of intractable Meniere's disease: a retrospective review with survey. Otol Neurotol 2013;34:1434-1437.

- 18. Committee on Hearing and Equilibrium. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of in Meniere's disease. Otolaryngol Head Neck Surg 1995;113:181-185.
- 19. Gurgel RK, Jackler RK, Dobie RA, Popelka GR. A new standardized format for reporting hearing outcome in clinical trials. Otolaryngol Head Neck Surg 2012;147:803-807.
- 20. Golub J, Ling L, Kaibao N, et al. Prosthetic implantation of the human vestibular system. Otol Neurotol 2014;35:136-147.
- 21. Phillips C, Defrancisci C, Ling L, et al. Postural responses to electrical stimulation of the vestibular end organs in human subjects. Exp Brain Res 2013:229:181-195
- 22. Derebery M, Fisher L, Berliner K, Chung J, Green K. Outcomes of endolymphatic shunt surgery for Meniere's disease: comparison with intratympanic gentamicin on vertigo control and hearing loss. Otol Neuro-
- 23. Pullens B, Verschuur H, van Benthem P. Surgery for Meniere's disease. Cochrane Database Syst Rev 2013;2:CD005395.
- 24. Cohen-Kerem R, Kisilevsky V, Einarson T, et al. Intratympanic gentamicin for Meniere's disease: a meta-analysis.  $Laryngoscope\ 2004;114:2085-2091.$
- Prezant T, Agapian J, Bohlman M, et al. Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness. Nat Genet 1993;4:289-294.
- 26. Chia S, Gamst A, Anderson J, Harris JP. Intratympanic gentamicin therapy for Meniere's disease: a meta-analysis. Otol Neurotol 2004;25:544-552.
- 27. Casani A, Cerchiai N, Navari E, Dallan I. Intratympanic gentamicin for Meniere's disease: short- and long-term follow-up of two regimens of treatment. Otolaryngol Head Neck Surg 2014;150:847–852.

  28. Boleas-Aguirre M, Sanchez-Ferrandiz N, Guillen-Grima F, Perez N. Long-
- term disability of class A patients with Meniere's disease after treatment with intratympanic gentamicin. Laryngoscope 2007;117:1474-1481.
- 29. Pyykko I, Eklund S, Ishizaki H, Aalto H. Postural compensation after intratympanic gentamicin treatment of Meniere's disease. J Vestib Res 1999;17:356-362.
- 30. Vibert D, Caversaccio M, Hausler R. Meniere's disease in the elderly. Otolaryngol Clin North Am 2010;43:1041-1046.
- 31. Sunde J, Gluth MB, Moore PC, et al. Delayed compensation following treatment of Meniere's disease with intratympanic gentamicin. Presented at the 49th Annual Spring Meeting American Neurotology Society. May
- 32. Patel M. Intratympanic corticosteroids in Ménière's disease: a mini-review. J Otol 2017;12:117-124.
- 33. Garduño-Anaya M, Couthino De Toledo H, Hinojosa-González R, Pane-Pianese C. Dexamethasone inner ear perfusion by intratympanic injection in unilateral Ménière's disease: a two-year prospective, placebo-controlled, double-blind, randomized trial. Otolaryngol Head Neck Surg 2005;133:
- 34. Casani A, Piaggi P, Cerchiai N, Seccia V. Intratympanic treatment of intractable unilateral Meniere disease: gentamicin or dexamethasone? A randomized controlled trial. Otolaryngol Head Neck Surg 2012;146:
- 35. Patel M, Agarwal K, Arshad Q, Hariri M. Intratympanic methylprednisolone versus gentamicin in patients with unilateral Ménière's disease: a randomised, double-blind, comparative effectiveness trial. Lancet 2016; 388:2753-2762
- 36. Leng Y, Liu B, Zhou R, Liu J. Repeated courses of intratympanic dexamethasone injection are effective for intractable Meniere's disease. Acta Otolaryngol 2017;137:154-160.
- 37. Martin-Sanz E, Esteban-Sanchez J, Rodrigañez-Riesco L, Sanz-Fernández R. Transitory effect on endolymphatic hydrops of the intratympanic steroids for Ménière's disease. Laryngoscope 2015;125: 1183-1188
- 38. Atrache Al Attrache N, Krstulovic C, Pérez Guillen V, Morera Pérez C. Response over time of vertigo spells to intratympanic dexamethasone treatment in Meniere's disease patients. J Int Adv Otol 2016;12:92-97.
- 39. Lavigne P, Lavigne F, Saliba I. Întratympanic corticosteroids injections: a systematic review of literature. Eur Arch Otorhinolaryngol 2016;273: 2271-2278
- 40. Liu YF, Xu H. The intimate relationship between vestibular migraine and Meniere disease: a review of pathogenesis and presentation. Behav Neurol 2016;2016:3182735.
- 41. Shin CH, Kim Y, Yoo MH, et al. Management of Meniere's disease: how does the coexistence of vestibular migraine affect outcomes? Otol Neurotol 2019;40(5):666-673.
- 42. Derebery MJ, Berliner KI. Allergy and its relation to Meniere's disease. Otolaryngol Clin North Am 2010;43:1047-1058.
- 43. Derebery MJ. Allergic and immunologic features of Meniere's disease. Otolaryngol Clin North Am 2011;44:655-666, ix.
  Weinreich HM, Agrawal Y. The link between allergy and Meniere's disease.
- Curr Opin Otolaryngol Head Neck Surg 2014;22:227-230.
- 45. Yang B, Brook CD. The role of allergy in otologic disease. Otolaryngol Clin North Am 2017;50:1091-1101.
- 46. Moon I, Park G, Choi J, et al. Predictive value of electrocochleography for determining hearing outcomes in Meniere's disease. Otol Neurotol 2012;
- Smith J. Noble H. Bias in research. Evid Based Nurs 2014;17:100–101.

Laryngoscope 130: October 2020