Comparison of Second-Echelon Treatments for Ménière's Disease

Gregory J. Basura, MD, PhD; Giant C. Lin, MD; Steven A. Telian, MD

IMPORTANCE To compare the efficacy of treatments commonly offered to patients with Ménière’s disease who fail conservative medical therapy including diuretics and a sodium-restricted diet.

OBJECTIVES This study compared three second-echelon treatments: the Meniett device, endolymphatic sac decompression, and intratympanic gentamicin injections to determine their comparative effectiveness and capacity to mitigate against the necessity of a surgical labyrinthectomy.

DESIGN, SETTING, AND PARTICIPANTS Retrospective observational study at an academic tertiary care center. Patients with Ménière’s disease who failed primary medical management were evaluated after treatment with a Meniett device (n=20), endolymphatic sac decompression (n=23) or intratympanic gentamicin injections (n=17). Cases were included if auditory and vertigo control data were available before and a minimum of two years after treatment, in patients without previous otologic surgery or intratympanic injections. Average age ranged from 54 to 75 years.

INTERVENTIONS Use of the Meniett device, endolymphatic sac shunt decompression surgery or intratympanic gentamicin injections using variable doses and injection schedules.

MAIN OUTCOMES AND MEASURES Proportion of patients with vertigo control and hearing preservation by a modified version of the AAO-HNS criteria after second-echelon treatment, thus not requiring definitive labyrinthectomy.

RESULTS Despite endolymphatic sac surgery demonstrating a longer duration (61 months) prior to labyrinthectomy, no differences were found between the 3 treatment options in terms of patients going on to definitive labyrinthectomy or in the number of months of symptom relief following treatment. There was also no difference in residual auditory perception across the 3 groups.

CONCLUSIONS AND RELEVANCE No significant therapeutic differences were found between the studied second-echelon treatments for symptom relief of Ménière’s disease.
 Ménière's disease (MD) is an idiopathic fluctuating disorder of the inner ear characterized by recurrent attacks of incapacitating vertigo, low-frequency sensorineural hearing loss, aural fullness, and tinnitus. First described in 1861 by Ménière, this disorder was believed to originate within the inner ear as a result of hydrops within the endolymphatic system. The resulting disruption of the inner ear function is thought to produce episodic attacks of vertigo and hearing loss. The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) Committee on Hearing and Equilibrium estimated that this condition affects 4.3 to 46 individuals per 100,000, with some geographic variation. The clinical course of MD is highly variable, but most patients experience spontaneous remission after a few years. Silverstein et al reported spontaneous resolution rates of 57% at 2 years and 71% at 8.3 years.

Despite its prevalence, the precise etiology of MD is unknown, and no definitive treatment reverses the symptoms. Treatment of the disorder has been associated with a significant placebo effect, and its relapsing, remitting nature has made evaluation of the various treatments challenging. Primary treatment includes a sodium-restricted diet and diuretic therapy. Other agents, including antihistamines, benzodiazepines, corticosteroids, and betahistine hydrochloride, have been used with mixed results, with approximately 60% to 87% of patients being symptom free for longer durations. For those patients with persistent incapacitating and disabling attacks after 3 to 6 months of conservative therapy and unilateral involvement, second-echelon interventions may be considered.

In patients with serviceable hearing (ie, speech reception thresholds [SRTs] better than 50.0 dB and word discrimination scores [WDSs] >80%), nonablative procedures have been advocated. Conversely, in those patients with no meaningful hearing, ablative treatments are often implemented, with the gold standard being transmastoid labyrinthectomy.

Second-echelon interventions may be categorized as those designed to affect the natural history of the disease with conservation of vestibular function (an intermittent low-pressure pulse generator device [Meniett; Medtronic ENT] and endolymphatic sac [ELS] decompression) and those designed to relieve symptoms by suppressing vestibular function or endolymph production (intratympanic gentamicin sulfate injections). The use of intermittent micropressure treatment administered via the low-pressure pulse generator device has been shown to be a safe and effective nonablative treatment option for MD relative to a placebo device after 4 months of use, with lasting results demonstrated after 2 years. Long-term symptom control was achieved in 67% (39 of 58) of patients who had class A (remission) or class B (significant improvement) vertigo. This treatment has been endorsed by a statement from the AAO-HNS Committee on Hearing and Equilibrium, which reads in part as follows: “We find that there is convincing and well-controlled medical evidence to support the use of micropressure therapy (such as the Meniett device) in certain cases of Ménière’s disease. Micropressure therapy can be used as a second level therapy when medical treatment has failed” (http://www.entnet.org/content/micropressure-therapy).

**Methods**

Access to medical records was granted following approval by the institutional review board of the University of Michigan Medical School, and all eligible cases consecutively treated from September 1990 through June 2010 were reviewed and are summarized in Table 1. The medical records were retrospectively reviewed, and all patient-identifying information was encrypted per institutional review board requirements to protect specific patient identity. A retrospective analysis comparing the efficacy of 3 second-echelon treatments was performed for patients with MD who had failed first-line therapy, including a sodium-restricted diet and diuretics. Treatment group assignments were determined by ordinary clinical practice, blending the judgment of the physician with the patient’s treatment priorities. Patients were included if they had a definite diagnosis of MD by AAO-HNS criteria, had experienced these symptoms in only one ear, and had received a second-echelon treatment of a trial of the intermittent low-pressure pulse generator device, ELS decompression, or intratympanic gentamicin injections. Those patients who began 1 of the 3 treatments at an outside facility, those who had less than 2 years of follow-up data at our institution, and those who had bilateral disease or previous ear surgery were excluded from...
Abbreviation: ELS, endolymphatic sac.

* The initial search string identified 1003 patients diagnosed as having Ménière’s disease. Ineligible patients were excluded based on bilateral disease, previous otologic surgery, or prior second-echelon treatment at an outside facility. The search then identified patients with whom each respective treatment was discussed or offered. Within each treatment group, the number of patients treated at our institution was determined.

The 3 groups were compared on the basis of age, sex, and percentage of patients who required subsequent definitive transmastoid labyrinthectomy within each treatment group. Audio- metrically, pretreatment and posttreatment comparisons of SRTs and WDSs were recorded using the last audiogram before the intervention compared with the final follow-up audiogram available for review. Because 2-year posttreatment audiograms were not consistently available, the final audiogram used in this study was often obtained many years after treatment and includes the last audiogram before transmastoid labyrinthectomy in those who required this surgery. To standardize the pretreatment and posttreatment audiometric outcomes, scattergrams for each treatment modality were constructed based on the proposed matrices by Gurgel et al.26 If data were available, the mean unilat eral weakness in the caloric responses to bithermal irrigations on videonystagmography at the time of initial treatment was recorded. For those who required subsequent definitive transmastoid labyrinthectomy within each group, the number of months after the initiation of second-echelon treatment before surgery was calculated.

The treatment schedule for the low-pressure pulse generator device was based on that used in a randomized, placebo-controlled, double-blind, multicenter trial of 4 months’ duration.15 As such, patients were instructed to use the device 3 times per day in the affected ear. Each treatment lasted 5 minutes, with 3 cycles each lasting for 1 minute of pressure pulses and for 40 seconds of pause. The pressure equalization tubes used for this study were Sheehy27 collar button or Paparella28 tubes.

Within the ELS decompression group, 19 of 23 patients included underwent ELS decompression by a surgeon who is not an author, with the remaining 4 being completed by 3 other surgeons (including S.A.T.). A review of the operative reports revealed that 19 individuals had complete ELS decompression, with all but one having a concurrent sigmoid sinus decompression. Complete ELS decompression in these patients is defined by a wide bony decompression technique that is preferred at our institution. Specifically, a wide bony decompression of the sac includes bone removal from the Donaldson line to the jugular bulb and from the sigmoid sinus to the operculum. The other 4 patients had a silastic ELS-mastoid shunt placed at the time of decompression. Of those who received a shunt, the sac lumen was entered distal to the operculum and was explored before silastic sheet placement as a shunt.

For the intratympanic gentamicin injections group, a common protocol across the 3 physicians (including S.A.T.) was used for each patient. A solution of gentamicin sulfate (40 mg/mL) was diluted with 1% lidocaine to yield a final concentration of gentamicin sulfate (36 mg/mL) that was injected into the middle ear (mean volume, 0.7 mL). The patient was positioned in a semirecumbent supine position with the head turned 45° away from the treated ear, and this was maintained after the injection for 20 to 30 minutes. The decision to perform additional injections, up to a maximum of 3 in this study, was based on the degree of symptom control and on patient treatment preference.

Individual participant data were entered into a spreadsheet (Excel; Microsoft Corporation) for statistical evaluation. For comparison of the percentage of patients in each group who required subsequent transmastoid labyrinthectomy, χ² test was performed. To compare the duration (in months) after second-echelon treatment in patients who required subsequent transmastoid labyrinthectomy, 1-way analysis of variance with Welch test was performed between the groups. Last, to compare the demographics and the effects of each treatment group on pre-SRTs and post-SRTs and WDSs, 1-way analysis of variance with Bonferroni post hoc multiple comparison test was performed using statistical software (SPSS; SPSS Inc).

**Results**

A total of 20 patients met inclusion criteria in the low-pressure pulse generator device group, with a mean age of 54.1 years, and 12 of them were female (Table 2). Within this group,
9 (45%) were categorized as class A, 5 (25%) were categorized as class B, and 6 (30%) were categorized as class C (Table 3). Of these, only 2 of 20 (10%) required subsequent transmastoid labyrinthectomy for intractable symptoms, with the mean time from the initiation of low-pressure pulse generator device treatment to transmastoid labyrinthectomy being 7.5 months (Figure 1). Before the use of the low-pressure pulse generator device, patients in this group had a mean SRT of 42.2 dB, with an 81% WDS on audiometric testing. On the final post-treatment audiogram, the mean SRT was 69.0 dB, with a 48% WDS (Figures 2, 3, and 4). On videonystagmography testing, the mean weakness of the ELS decompression group on caloric irrigations was not abnormal at 15%.

A total of 23 patients met inclusion criteria in the ELS decompression group, with a mean age of 60.0 years, and 16 of them were female (Table 2). Within this group, 5 (22%) required subsequent transmastoid labyrinthectomy for intractable symptoms, with the mean time from ELS decompression to transmastoid labyrinthectomy being 61.0 months (Figure 1). Patients in this group had a mean SRT of 45.5 dB, with a 79% WDS before ELS decompression, and a final post-treatment SRT of 64.0 dB, with a 42% WDS (Figures 2, 3, and 4). On videonystagmography testing, the mean weakness of the ELS decompression group on caloric irrigations was not abnormal at 15%.

A total of 17 patients met inclusion criteria in the intratympanic gentamicin injection group, with a mean age of 75.3 years, and 10 of them were female (Table 2). This group was older and had statistically poorer word discrimination before treatment, suggesting a predisposition to offer this modality to older individuals with more advanced hearing loss at the
time of medical failure (Figures 2 and 3). The mean number of injections administered was 1.9. Within this group, 7 (41%) were categorized as class A, 5 (29%) were categorized as class B, and 5 (29%) were categorized as class C (Table 3). Of these, 4 of 17 (24%) required subsequent transmastoid labyrinthectomy for intractable symptoms, with the mean time from the first intratympanic gentamicin injection to transmastoid labyrinthectomy being 9.0 months (Figure 1). Before injection, patients in this group had a mean SRT of 55.6 dB, with a 53% WDS on audiometric testing, and a posttreatment SRT of 64.4 dB, with a 46% WDS (Figures 2, 3, and 4). The pretreatment WDS in the intratympanic gentamicin injections group was significantly poorer ($P < .006$) compared with the pretreatment scores in the other 2 groups, yet their posttreatment scores did not differ significantly (Figure 3). On videonystagmography testing, the mean weakness of the intratympanic gentamicin injections group was found to be significant at 49%.

Although the ELS decompression group had the longest duration of patient posttreatment leading up to subsequent transmastoid labyrinthectomy, Kaplan-Meier survival analysis demonstrated no significant differences between the 3 treatment groups (Figure 5). No statistically significant differences were found between the 3 second-echelon treatment options in terms of the percentage of patients requiring subsequent definitive transmastoid labyrinthectomy or in the number of months between treatment and transmastoid labyrinthectomy. Despite deterioration of hearing over time in all treatment groups, no significant differences were observed in the effect on auditory perception between the 3 groups.

**Discussion**

The present study demonstrated various degrees of vertigo control using 3 clinically accepted second-echelon treatments for patients with MD who had failed initial medical management. Transmastoid labyrinthectomy was avoided in at least 75% of patients in each group: 4 of 17 had labyrinthectomy in the gentamicin group, 2 of 20 had labyrinthectomy in the low-pressure pulse generator device group, and 5 of 23 had labyrinthectomy in the ELS decompression group. Although the
low-pressure pulse generator device group had the highest percentage (90% [18 of 20]) of patients choosing not to pursue ablative surgery, no statistically significant differences were noted in this modest sample size with regard to preventing the need for transmastoid labyrinthectomy. It seems reasonable to suggest that the use of the low-pressure pulse generator device compares favorably with ELS decompression and intratympanic gentamicin injections in cost, and it is superior in patient safety. However, this modality requires ongoing compliance with active treatment administration 3 times daily for a period of weeks or months, which could be less desirable to some than a single medical or surgical intervention. Experience suggests that most patients with this disorder are highly motivated to participate in their recovery process, and many prefer an option that may avoid the risks of surgery or intratympanic injections. This consideration continues to suggest that the low-pressure pulse generator device is an important option in the treatment of this disorder, even as the mechanism of its action is being better elucidated. Our findings are consistent with reports that hearing did not improve with short-term or long-term use of the device, while other investigators have reported mild improvements in auditory outcomes. The safety and efficacy of the low-pressure pulse generator device make this a particularly attractive feature for treating bilateral disease, in which the choice of treatment is often difficult given the limited therapeutic options available.

The ELS decompression group showed the longest duration elapsing before transmastoid labyrinthectomy. Such an outcome might be expected partially based on an anticipated disinclination of patients to undergo consecutive surgical procedures within a short interval. This operation was more frequently used in our clinical practice before the less invasive options became available as alternative second-echelon treatments; therefore, much longer cumulative follow-up data are available. This raises the concern that failure rates in the other groups may have been underestimated because of shorter follow-up periods. However, as demonstrated in the Kaplan-Meier analysis, the failures in the intratympanic gentamicin injections and low-pressure pulse generator device groups tended to occur early, with no late failures noted in either group after longer than 5 years of observation. This suggests that lasting remissions were reliably obtained among responders. In this regard, it is noteworthy that ongoing late relapses occurred in the surgical group, suggesting that long-term vertigo control may be less durable with ELS decompression, although early results may be favorable. Our data demonstrated that 65% of patients achieved a class A (13% [3 of 23]) or class B (52% [12 of 23]) designation, as seen in prior studies, following ELS decompression. However, although all 3 of our treatment groups had similar percentages of failures (range, 29% [5 of 17] to 35% [8 of 23]), the ELS decompression group had the poorest rate of complete control of vertigo (class A results), with only 13% (3 of 23) vs 41% (7 of 17) and 45% (9 of 20) for the other 2 modalities. Our surgical population consisted primarily of patients having complete ELS decompression, with shunt placements performed in only 4 of 23 cases at one surgeon’s discretion. Prior investigations have not consistently demonstrated significant differences between endolymphatic mastoid shunt vs complete sac decompression alone in reducing vertigo attacks, with improvement in 67% vs 66% of patients with MD. In 2 larger uncontrolled retrospective studies, Derebery et al reported 77% improvement in symptoms using sac decompression with an ELS-mastoid shunt, while Arenberg reported a 74% elimination of vertigo symptoms in 214 shunt cases. Overall, the available data suggest that decompressions with and without shunting are similarly efficacious, although uncontrolled data suggest that a slight advantage may be obtained when a shunt is placed. While the present study shows a longer delay before resorting to transmastoid labyrinthectomy among ELS decompression failures, this may be at least partially attributable to a patients’ understandable reluctance to undergo a second operative intervention within a short time frame. When the present data are considered in light of the available evidence and cost considerations, one may state that ELS decompression is an acceptable, but not superior, second-echelon treatment option.

In the present study, 70% of patients achieved class A (41% [7 of 17]) or class B (29% [5 of 17]) status for vertigo control following intratympanic gentamicin injections. In this group, 24% (4 of 17) of patients required subsequent transmastoid labyrinthectomy for intractable or persistent symptoms, with the mean time from the first intratympanic gentamicin injections to transmastoid labyrinthectomy being 9.0 months. No significant detrimental effects on audiologic performance were observed up to 2 years following treatment compared with the other treatment options studied. These data are consistent with published meta-analyses of intratympanic gentamicin injections showing complete or significant vertigo control in most patients treated. Controversy remains regarding protocols that use multiple injections vs those that use additional intratympanic gentamicin injections only if needed for persistent or recurrent vertigo. Chia et al showed that a high-dose or multiple-dose technique (3 doses daily for 4 days) led to increased rates of hearing loss (35%) and vertigo (67%) ($P < .001$). Alternatively, low-dose titration techniques (1-2 doses, with repeated treatment based on persistent symptoms) were associated with lower rates of hearing loss (23%) but reduced vertigo control (67%). Gabra and Saliba used a method of single-dose intratympanic gentamicin injection once per week for 4 weeks. They demonstrated the lowest reported rates of hearing loss (13%), with complete vertigo control in approximately 75% of patients. In our study, patients received injections that were given on a monthly basis and titrated as needed to achieve vertigo control.

Dietary sodium restriction with concomitant diuretic use is effective as an initial treatment strategy in up to 79% of patients with MD. Despite this and the anticipated high rates of spontaneous remission in MD, many patients require therapeutic intervention for control of disabling vertigo attacks. Definitive treatment for recalcitrant attacks of vertigo in unilateral MD remains surgical transmastoid labyrinthectomy. This operation results in control of episodic vertigo by unilateral ablation of peripheral vestibular function, but at the cost of any residual hearing. Of course, unilateral vestibular ablation with hearing preservation may be achieved with the use of vestibular neurectomy, although this is much less commonly per-
formed than in the last 2 decades of the past century. The recognition of long-term hearing deterioration from the underlying disorder and the relative safety of intratympanic gentamicin injections have essentially made vestibular neurectomy obsolete. Intermediate options short of peripheral vestibular deafferentation, herein called second-echelon interventions, are widely accepted but are still inadequately studied procedures that aim to preserve hearing, while controlling vertigo. Larger-scale comparative effectiveness studies designed with sufficient power to discriminate among these treatment options are warranted.

Overall, the present findings support the null hypothesis that none of the second-echelon treatment strategies in MD are clearly superior to the others at achieving symptom relief or reducing the need for transmastoid labyrinthectomy. These findings are admittedly constrained by the high rate of improvement in all groups and the modest statistical power of the available sample but provide demographic data and treatment effect sizes needed to allow for sample size calculations to support a larger prospective multi-institutional trial. Based on the findings of this retrospective review, we intend to initiate a large multi-institutional comparative effectiveness trial incorporating longitudinal audiometric, vestibular, and quality-of-life measures in patients with MD. Such a study is needed to obtain a sample size adequate to distinguish any clinically significant therapeutic advantages among the various treatment modalities available. We anticipate conducting a pragmatic study using a noninferiority statistical approach, most likely using a cluster design with treatment assignment based on treatment site rather than randomizing individual enrolled participants. The strength of such a design is a high rate of accrual and results that are generalizable across a wide variety of practice settings. It seems to be feasible to conduct this study via the Creating Healthcare Excellence Through Education and Research network,39 a 30-site practice-based clinical research network that is poised to complete such endeavors. These include general otolaryngology practices, as well as private and academic neuro-otology practices. A survey of these sites yielded favorable responses from 22 participating centers, representing 88 otolaryngologists who treat MD, among whom 39 were neuro-otologists. More than 80% of these centers are offering ELS decompression (about 60 cases annually) and intratympanic gentamicin injections (about 135 cases per year). Ten centers are already offering the low-pressure pulse generator device, treating about 35 cases per year. Using the estimates from this survey, along with clinical demographic data available from a subset of the participating centers in the Creating Healthcare Excellence Through Education and Research network, this study should accrue at least 100 eligible patients with MD annually. Assuming less than a 15% dropout rate, this comparative effectiveness trial would require less than 3 years to accrue sufficient participants and approximately 5 years to obtain 2-year follow-up data per AAO-HNS criteria3 and analyze the data for publication of treatment results.

Conclusions

Clinical studies of relapsing, remitting disorders such as MD are fraught with difficulty because of the phenomenon of symptom regression regardless of treatment assignment. As such, little evidence supports the choice of any particular second-echelon treatment for patients who have failed initial conservative therapy for this disorder. The 3 treatment modalities studied herein provided meaningful relief of vertigo in most participants, and the need for transmastoid labyrinthectomy was obviated in 75% to 90% of individuals: 4 of 17 had labyrinthectomy in the gentamicin group, 2 of 20 had labyrinthectomy in the low-pressure pulse generator device group, and 5 of 23 had labyrinthectomy in the ELS decompression group. Endolymphatic sac decompression had the lowest success rate in achieving complete control of episodic vertigo. The low-pressure pulse generator device was not inferior to the more widely accepted options and compares favorably with regard to cost and short-term risk to the patient. Progression of hearing loss in this population seems to be inexorable regardless of the treatment modality selected, suggesting that a more ideal treatment remains elusive.

REFERENCES

10. Santos PM, Hall RA, Snyder JM, Hughes LF, Dobe RA. Diuretic and diet effect on Ménérie’s
Second-Echelon Treatments for Ménière’s Disease

Original Investigation Research

Hearing and Equilibrium guidelines.


