The Laryngoscope

TRIOLOGICAL SOCIETY CANDIDATE THESIS

Hearing Results and Quality of Life After Streptomycin/ Dexamethasone Perfusion for Meniere's Disease

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Objectives/Hypothesis: To evaluate the hearing changes and quality-of-life outcomes of 393 cases of streptomycin/ dexamethasone inner ear perfusion performed by the primary author on 312 ears of 299 patients with Meniere's disease between July 2002 and May 2010.

Study Design: Retrospective chart review.

Methods: Objective arm: A database was used to compile pretreatment and post-treatment audiograms as well as basic demographic information, dates of treatment, number of treatments, and which ear was treated. All patients met the 1995 American Academy of Otolaryngology–Head and Neck Surgery Committee on Hearing and Equilibrium Guidelines for the diagnosis and evaluation of therapy in Meniere's disease. All patients underwent one or more 3-day treatments consisting of daily intratympanic injections of a low-dose streptomycin/high-dose dexamethasone mixture plus intravenous dexamethasone. The end point for treatment was adequate control of vertigo. Subjective arm: The Meniere's Disease Outcomes Questionnaire survey was used to assess patients' quality of life after receiving streptomycin/dexamethasone inner ear perfusion. All procedures were performed by the primary author at the Shea Ear Clinic, a tertiary-referral otology clinic and outpatient surgery center.

Results: After a single 3-day treatment, the average change in pure tone average was 0.89 dB (±11). The average change in word recognition score was 0.49% (±17). The average number of days from treatment to follow-up audiogram was 94 with a range of 8 to 1,603. Clinically significant hearing loss occurred after 62 of 393 (15.7%) treatments. Severe hearing loss occurred after 20 of 393 treatments (5.0%). The percentage of ears with clinically significant hearing loss after all treatments was 56 of 312 (17.9%). A total of 215 surveys were returned from 383 patients (56.1%) to whom they were mailed. There were 90% of patients who indicated improvement in quality of life after treatment and 88% who indicated improvement in their ''vertigo subscore,'' a domain within the survey that focuses on vertigo control.

Conclusions: Streptomycin/dexamethasone inner ear perfusion is as safe to the hearing of patients with Meniere's disease as other aminoglycoside regimens and provides a significant improvement in quality of life.

Key Words: Meniere's, streptomycin, gentamicin, aminoglycoside, perfusion.

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INTRODUCTION

Meniere's disease (MD) is the clinical syndrome of endolymphatic hydrops and typically causes symptoms of vertigo, aural fullness, hearing loss, and tinnitus. The first line of treatment has traditionally been medical management, which includes a sodium-restricted diet, diuretics, vestibular suppressants, antiemetics, and systemic steroids. Medical therapy has been a mainstay for treatment of MD for many years, but some have questioned its utility.[1] Ruckenstein et al. found that further analysis of several studies evaluating diuretic therapy failed to demonstrate any real benefit.[2] For medically refractory patients, however, several surgical approaches are used. Endolymphatic sac procedures have a reported success rate of 64.5% to 78% and a hearing preservation rate of 66.7%[3,4] but are somewhat controversial because of a perceived placebo effect,[5,6] a failure rate of 30% at 5 years,[2] and the fact that they do not stabilize hearing loss. Vestibular nerve section has been described by some as the "gold standard" for control of vertigo in MD, with a quoted success rate of 95%,[7] but requires a middle or posterior fossa craniotomy with the attendant risks and possible complications. For MD patients without serviceable hearing, surgical labyrinthectomy controls vertigo by removing the vestibular end organs. "Chemical labyrinthectomy" via intratympanic perfusion with high-dose aminoglycosides, that is, 120 mg/mL streptomycin, which is not the goal of the treatment reported here, is also effective in controlling vertigo in stage IV MD[8] and is much simpler to perform than surgical labyrinthectomy.

Corticosteroids are useful in the treatment of MD because of their anti-inflammatory properties, as MD is believed by many to be immune mediated. Side effects such as adrenal suppression limit the amount that can

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Dedicated to the memory of Grant W. Somes, PhD, our friend and colleague, who contributed to this study and passed away March 11, 2010.

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be given systemically, and the blood-labyrinthine barrier limits the amount reaching the perilymph. The intratympanic route offers a convenient way to deliver a higher concentration of steroid to the perilymph than can be achieved by giving it orally or systemically.[9] Several studies have demonstrated benefit in patients in earlier stages of MD in the form of stabilizing or improving fluctuating hearing levels and improvement in aural fullness and dizziness.[10–12] Intratympanic perfusion with aminoglycosides has become the treatment of choice for MD in the last 2 decades because of its efficacy and convenience, and some have speculated that it could possibly replace vestibular surgery.[13]

This article is a retrospective analysis of 393 cases of streptomycin/dexamethasone inner ear perfusion (SDIEP) performed on 312 ears of 299 MD patients by the primary author at the Shea Ear Clinic between July 2002 and May 2010 using a mixture of low-dose streptomycin (10 mg/mL) and high-dose dexamethasone (24 mg/mL) in a hyaluronan vehicle, given once daily for 3 consecutive days, along with 16 mg of intravenous dexamethasone each day. This "combination therapy" was designed to harness the beneficial effects of both agents and improve safety for the hearing. The end point for treatment in this study was satisfactory subjective control of vertigo only, as it was shown by Light et al. that 100% reduced vestibular response to ice water caloric stimulation is not necessary to achieve adequate control in many patients.[14] Additional treatments were offered to patients as needed to achieve this goal. This form of titration therapy has resulted in a low rate of hearing loss, good control of vertigo, and a high rate of acceptance by patients. The concept of low-dose aminoglycoside therapy has also been advocated by others.[15] Because every study has demonstrated improvement in dizziness in the vast majority of patients,[13] this report, like some others,[16] focused on hearing. The aim is to demonstrate that SDIEP is safe to hearing and effective at improving dizziness and quality of life (QOL) in MD patients. As such, it can be offered early in the course of therapy without requiring patients to submit to a prolonged medical regimen first.

Improvement in vertigo is more difficult to quantify than change in hearing. This is partially because the 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) Committee on Hearing and Equilibrium (CHE) Guidelines[17] do not take into account the severity of vertigo episodes, only the number. Several studies have shown that MD patients experience significant deterioration in mental and physical health and well-being.[18–20] Other studies have demonstrated a definite improvement in QOL following aminoglycoside therapy.[21]

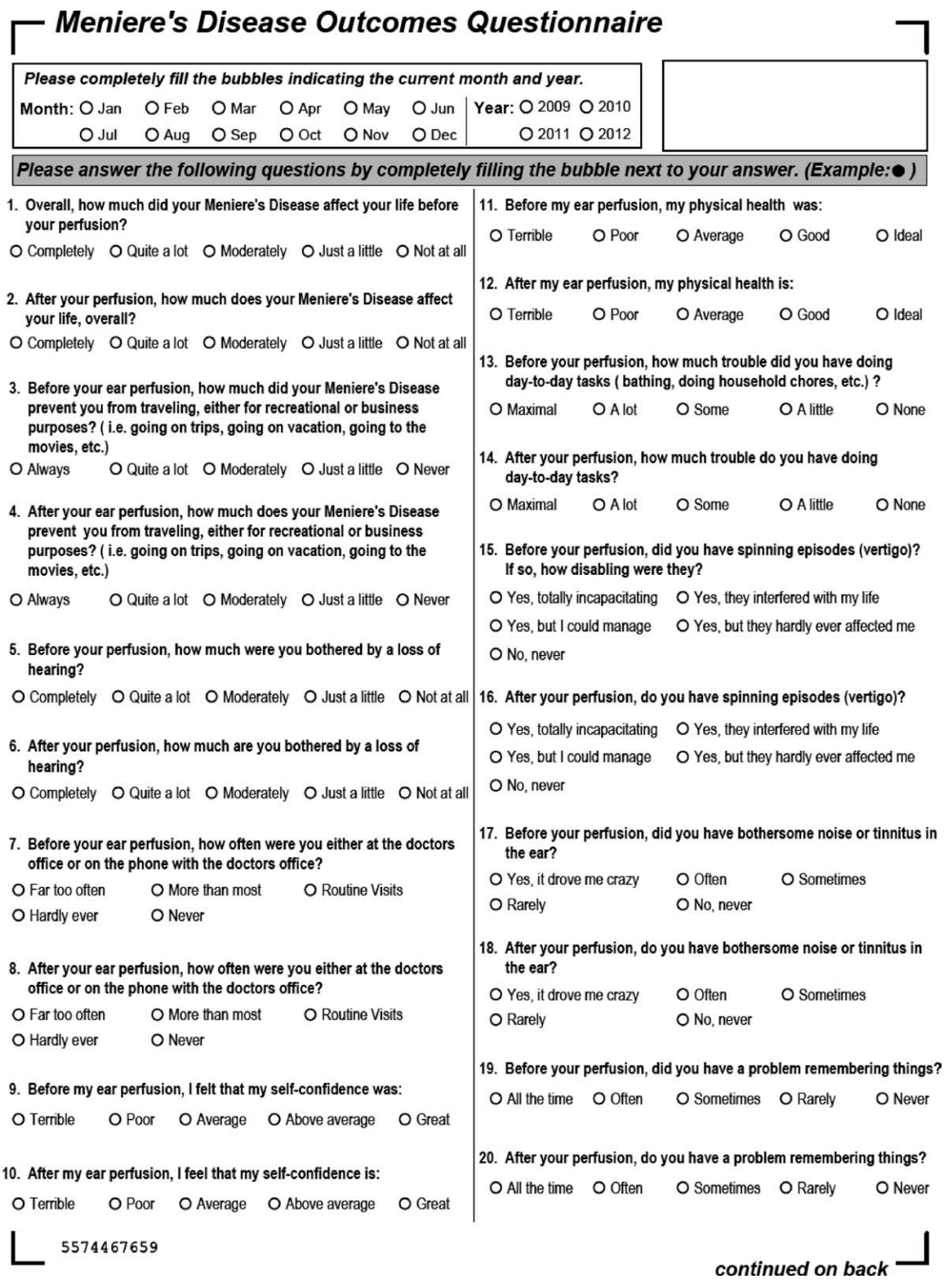
The Meniere's Disease Outcomes Questionnaire (MDOQ) is a validated QOL survey for patients that have undergone treatment for MD (Fig. 1). Using this survey, Kato et al. found that 87% of patients had an improvement in QOL after endolymphatic sac decompression.[22] Others have used the MDOQ to evaluate streptomycin perfusion[23] and surgical labyrinthectomy[24] and have found that both are highly effective at improving QOL. The MDOQ focuses on how MD affects the patient's life, functioning, and overall well-being in three domains: physical, mental, and social. It was adapted for use in this study with permission from its author, with the only change being that "perfusion" was used in place of "surgery."

MATERIALS AND METHODS

Patients recommended for SDIEP had "definite" or "probable" MD according to the 1995 AAO-HNS CHE Guidelines. All patients had previously tried medical therapy without adequate improvement. Audiologic workup included pure-tone and speech audiometry, electrocochleography, and video electronystagmography. Magnetic resonance imaging was used to rule out retrocochlear pathology if suspected. A summating potential—to—action potential ratio of 0.40 or higher on the electrocochleogram is considered evidence of endolymphatic hydrops[25] and is used at the Shea Ear Clinic, although some have suggested that a value of 0.30 or higher may suggest hydrops.[26] Audiograms were obtained before each SDIEP and at each follow-up visit. When vertigo control was judged to be inadequate at follow-up, another SDIEP was generally offered. The interval, an average of 94 days, allows sufficient time for the patient to recover from the transient disequilibrium that many of them experience following SDIEP as well as for any potential effects on hearing to become apparent. Most patients received one to three SDIEPs over varying periods of time, depending on their response.

The protocol consists of once-daily injections into the middle ear of a solution of 10 mg/mL streptomycin sulfate plus 24 mg/mL dexamethasone in a hyaluronan vehicle, which is mixed by a compounding pharmacy. All SDIEPs were performed by the primary author at the Shea Ear Clinic's outpatient surgery center. A 3-day sequence is considered one SDIEP. Patients are given 16 mg of dexamethasone intravenously each day unless medically contraindicated. Patients are premedicated with 5 mg of midazolam intravenously each day before SDIEP. Before the first injection, two small holes are made in the tympanic membrane over the round window niche using an argon laser (Lumenis Novus Spectra, Santa Clara, CA) at 2.0 W and 0.5-second pulse duration, and this is the only discomfort felt by the patient. One hole is used for injection and the other to allow air to escape as the middle ear is slowly filled using a blunt 22-gauge needle. The holes remain open for 3 days, avoiding the need to puncture the drum again on the second and third day. A ventilation tube is generally not inserted. Approximately 0.3 to 0.4 mL of perfusate is required to fill the middle ear. Following injection, the patient is instructed to lie with the treated ear up for 2 hours and minimize talking and swallowing. The protocol has proven safe and effective and is widely accepted by patients.

A database was created using Filemaker Pro 10.0.3 (Filemaker, Inc., Santa Clara, CA) for the hearing (objective) and QOL survey (subjective) results. Demographic information included sex, date of birth, date of initial visit, diagnosis, first ear involved with MD, and date of each SDIEP. Patients were identified only by their medical record number. Audiometric data including air conduction thresholds and word recognition scores (WRSs) were recorded in the database for each pretreatment and post-treatment audiogram in the patient's medical record. Four-tone pure tone averages (PTAs) were calculated according to the 1995 AAO-HNS CHE Guidelines. For each ear of each patient, the SDIEP treatments were assigned a sequence number in their order of occurrence. Each sequence consisted of a pretreatment audiogram, a 3-day SDIEP procedure, and a post-treatment audiogram. The pretreatment audiogram was always the last one before SDIEP, and the post-treatment audiogram was always the first one after SDIEP. No audiograms performed outside the



Meniere's Disease Outcomes Questionnaire

Please completely fill the bubbles indicating the current month and year.

Month: O Jan O Feb O Mar O Apr O May O Jun O Jul O Aug O Sep O Oct O Nov O Dec

Year: O 2009 O 2010 O 2011 O 2012

Please answer the following questions by completely filling the bubble next to your answer. (Example:●)

1. **Overall, how much did your Meniere's Disease affect your life before your perfusion?**
   O Completely O Quite a lot O Moderately O Just a little O Not at all

2. **After your perfusion, how much does your Meniere's Disease affect your life, overall?**
   O Completely O Quite a lot O Moderately O Just a little O Not at all

3. **Before your ear perfusion, how much did your Meniere's Disease prevent you from traveling, either for recreational or business purposes? (i.e. going on trips, going on vacation, going to the movies, etc.)**
   O Always O Quite a lot O Moderately O Just a little O Never

4. **After your ear perfusion, how much does your Meniere's Disease prevent you from traveling, either for recreational or business purposes? (i.e. going on trips, going on vacation, going to the movies, etc.)**
   O Always O Quite a lot O Moderately O Just a little O Never

5. **Before your perfusion, how much were you bothered by a loss of hearing?**
   O Completely O Quite a lot O Moderately O Just a little O Not at all

6. **After your perfusion, how much are you bothered by a loss of hearing?**
   O Completely O Quite a lot O Moderately O Just a little O Not at all

7. **Before your ear perfusion, how often were you either at the doctors office or on the phone with the doctors office?**
   O Far too often O More than most O Routine Visits
   O Hardly ever O Never

8. **After your ear perfusion, how often were you either at the doctors office or on the phone with the doctors office?**
   O Far too often O More than most O Routine Visits
   O Hardly ever O Never

9. **Before my ear perfusion, I felt that my self-confidence was:**
   O Terrible O Poor O Average O Above average O Great

10. **After my ear perfusion, I feel that my self-confidence is:**
    O Terrible O Poor O Average O Above average O Great

11. **Before my ear perfusion, my physical health was:**
    O Terrible O Poor O Average O Good O Ideal

12. **After my ear perfusion, my physical health is:**
    O Terrible O Poor O Average O Good O Ideal

13. **Before your perfusion, how much trouble did you have doing day-to-day tasks (bathing, doing household chores, etc.) ?**
    O Maximal O A lot O Some O A little O None

14. **After your perfusion, how much trouble do you have doing day-to-day tasks?**
    O Maximal O A lot O Some O A little O None

15. **Before your perfusion, did you have spinning episodes (vertigo)? If so, how disabling were they?**
    O Yes, totally incapacitating O Yes, they interfered with my life
    O Yes, but I could manage O Yes, but they hardly ever affected me
    O No, never

16. **After your perfusion, do you have spinning episodes (vertigo)?**
    O Yes, totally incapacitating O Yes, they interfered with my life
    O Yes, but I could manage O Yes, but they hardly ever affected me
    O No, never

17. **Before your perfusion, did you have bothersome noise or tinnitus in the ear?**
    O Yes, it drove me crazy O Often O Sometimes
    O Rarely O No, never

18. **After your perfusion, do you have bothersome noise or tinnitus in the ear?**
    O Yes, it drove me crazy O Often O Sometimes
    O Rarely O No, never

19. **Before your perfusion, did you have a problem remembering things?**
    O All the time O Often O Sometimes O Rarely O Never

20. **After your perfusion, do you have a problem remembering things?**
    O All the time O Often O Sometimes O Rarely O Never

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continued on back

Fig. 1. Meniere's Disease Outcomes Questionnaire.

Shea Ear Clinic were used in the study. When additional audiograms were available, they were included in the database, although only pretreatment and post-treatment audiograms were used to assess changes in hearing. It was assumed that hearing loss from SDIEP ototoxicity would be observed in the first post-treatment audiogram. The number of days from each SDIEP to the post-treatment audiogram was also calculated and is reported in the column "Days proc to posttest" in the Supporting

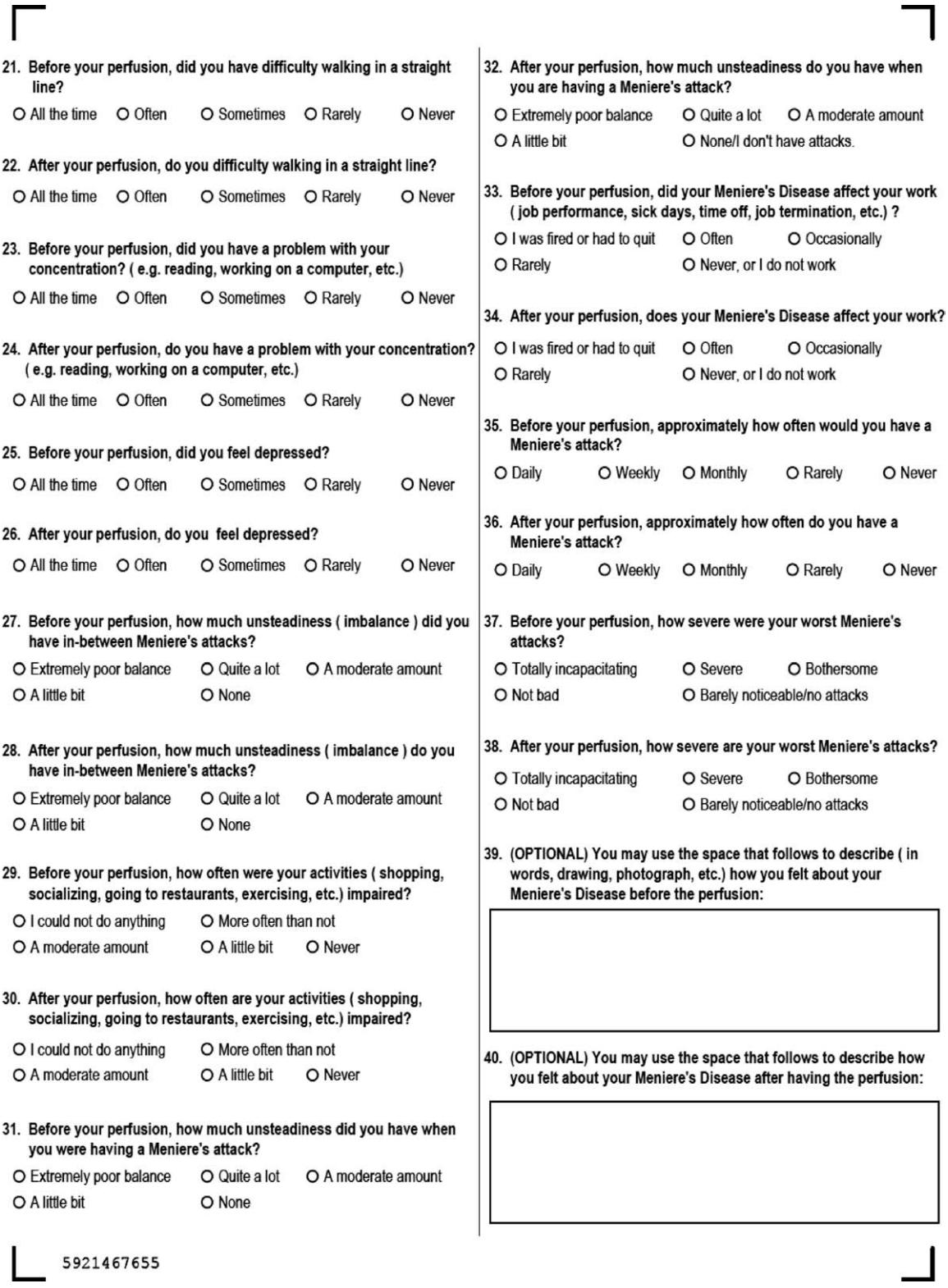

Fig. 1. Continued

Information section available online. The patient's pretreatment and post-treatment MD stage, according to the 1995 AAO-HNS CHE criteria, was also reported.

The MDOQ consists of 40 questions that are paired for the pretreatment and post-treatment condition. The first 38 questions are 19 multiple-choice question pairs that focus on the patient's mental, physical, and social well-being. The first question pair is a "global" question that was designed by Kato et al. to evaluate the validity of the MDOQ as an outcomes tool by assessing the correlation between the change in the MDOQ

TABLE I.
Number of Patients in Each Meniere's Stage Before First and After Last Streptomycin/Dexamethasone Inner Ear Perfusion.

	Meniere's Stage			
	1	2	3	4
Before first SDIEP, no. (%)	123 (39.4)	48 (15.4)	120 (38.5)	21 (6.73)
After last SDIEP, no. (%)	115 (36.9)	57 (18.3)	114 (36.5)	26 (8.33)

SDIEP = streptomycin/dexamethasone inner ear perfusion.

QOL score and the change in the global question score. The last question pair is an optional "fill in the blank" area that is included for any additional patient commentary. Answers on the survey are given a numeric score from 0 to 4. The pretreatment scores were calculated according the following formula: pretreatment QOL score = sum of pretreatment question scores/maximum possible pretreatment scores × 100. The post-treatment scores were calculated in the same fashion. A higher post-treatment score indicates improvement in QOL. The survey was mailed to 383 patients identified as eligible to be included in the study, and 215 surveys were returned (56.1%). Many surveys had missing items, but a total of 56 were completed fully. Questions 15, 35, and 37, concerning pretreatment vertigo, along with the corresponding post-treatment questions, 16, 36, and 38, were analyzed independently and used to calculate a "vertigo subscore," in lieu of more objective data about vertigo control, which was not consistently available in this retrospective analysis. In addition, subscores in the three other domains, mental, physical, and social health, are reported. Correlation between QOL outcomes, number of SDIEPs, and change in PTA and WRS was also analyzed.

RESULTS

This study attempted to include every case of SDIEP performed by the primary author between July 2002 and May 2010, and a total of 674 cases of SDIEP were identified. Of these, 393 had audiometric data that was sufficiently complete to allow preprocedure to post-procedure comparisons. This represented 312 ears of 299 patients, of whom 131 were male (43.8%) and 168 female (56.1%). Their average age was 57 years (range, 18–90). The numbers of patients in each MD stage before their first and after their last SDIEP are shown in Table I. The average changes in PTA and WRS after a single SDIEP were 0.89 dB (±11) and 0.49% (±17), respectively. A total of 62 of 393 (15.7%) SDIEPs resulted in "clinically significant" hearing loss (a change in PTA of 10 dB or more or a change in WRS of 15% or more, according to the 1995 AAO-HNS CHE criteria) by their follow-up audiogram. Twenty of 393 (5.0%) SDIEPs resulted in severe hearing loss (a change in PTA of 30 dB or more or a change in WRS of 30% or more, the author's own criteria) by their follow-up audiogram. After all SDIEPs were completed, 56 of 312 (17.9%) ears had clinically significant hearing loss by the CHE criteria. The average time from SDIEP to follow-up audiogram was 94 days, with a range of 8 to 1,603 days. Thirteen of 299 patients (4.3%) underwent bilateral SDIEP, although never at the same time, with the exception of one patient who had bilateral MD and a total of six SDIEPs on each ear over 22 months. The last five were simultaneous bilateral SDIEPs performed at the patient's insistence. After numerous lengthy discussions about the risks of and options for treatment, the patient was insistent that SDIEP gave her significant, although temporary, improvement in her dizziness and overall condition, even though her hearing deteriorated.

Table II shows the number of ears that underwent one to six SDIEPs. The pretreatment mean QOL score, post-treatment mean QOL score, mean change in QOL, and P value of each are listed in Table III. Questions 1 and 2 are the "global" question pair and an internal control to correlate with and validate the results of the remaining questions, 3 to 38. Questions 9, 10, 19, 20, 23, 24, 25, and 26 are the mental health domain. Questions 5, 6, 11, 12, 15, 16, 17, 18, 21, 22, 27, 28, 31, 32, 35, 36, 37, and 38 are the physical health domain. Questions 3, 4, 7, 8, 13, 14, 29, 30, 33, and 34 are the social health domain. Questions 15, 16, 35, 36, 37, and 38 are the "vertigo subscore" domain, which was designated to assess vertigo control specifically. Table IV lists the percentages of patients who were improved, unchanged, and worse, in each domain. A number of correlations between the objective audiometric data and the subjective QOL data were examined, but most did not reach statistical significance. One comparison that did was the number of SDIEPs in a single ear and the change in PTA for that ear (Spearman correlation coefficient of 0.13, $P = .0289$) (Fig. 2). Also, there was very significant correlation (Spearman correlation coefficient of 0.76, $P < .0001$) between the results of the "global" question pair and the MDOQ survey as a whole.

DISCUSSION

Streptomycin was the first aminoglycoside and was used to treat tuberculosis in the 1940s. Its ototoxicity was harnessed by Fowler, Hawkins and Lurie, and Schuknect to treat vertigo and MD[27–29] but with high rates of hearing loss. Beck and Schmidt observed that much lower doses of streptomycin or gentamicin could be used to ablate only the secretory mechanism and not the vestibular organ and were able to alleviate dizziness in 92.5% of patients with only 15% "deteriorated" hearing and "none deafened."[30] Shea reduced the dose of streptomycin to 25 μg, introduced it through a fenestration in the lateral semicircular canal, and reported excellent control of vertigo with hearing "a little worse" in 20% and "much worse" in only 5%.[31] Further refinements were made by Nedzelski et al., who used 26.7 mg/mL of gentamicin three times a day until nystagmus was observed, unsteadiness and gait instability developed, hearing worsened, or

TABLE II.
Number of Ears That Had One to Six Streptomycin/Dexamethasone Inner Ear Perfusion Treatments.

	No. of SDIEPs					
	1	2	3	4	5	6
No. of ears (%)	236 (78.9)	45 (15.1)	12 (4.0)	5 (1.7)	0 (O)	2 (0.3)
Total, %	78.9	94.0	98.0	99.7	99.7	100.0

SDIEP = streptomycin/dexamethasone inner ear perfusion.

after 12 doses were administered. He reported 83% control of vertigo and 10% profound hearing loss.[32] Minor used the same concentration and similar end points in a weekly dosing regimen and reported a vertigo control rate of 91% with only 3% profound hearing loss.[33] These studies explored the concept of "subablation," which did not have complete destruction of vestibular function as a goal. Several studies found that aminoglycoside therapy could actually improve hearing in some patients,[34] most likely from the effect on the secretory function of the dark cells in the stria vascularis.[8,35,36] Beck and Schmidt found that total ablation, as evidenced by absent ice-water calorics, was not required to control vertigo and that when it was used as the end point, severe to profound hearing loss developed in 58% of patients.[30]

Many investigators began to use gentamicin rather than streptomycin because of its availability. Streptomycin had become difficult to obtain, and there was a perception from earlier studies that it was associated with a high rate of hearing loss. Both drugs are certainly cochleotoxic at higher doses, but there is debate as to which is superior in terms of its ability to selectively ablate vestibular function with the least effect on cochlear function or even whether either drug is selectively vestibulotoxic at all.[37,38] Many recent studies claim that gentamicin is the "drug of choice" for inner ear perfusion, but others contradict this.[39–41] In the only study that has directly compared them, Norris et al. found streptomycin to be more selectively vestibulotoxic and less cochleotoxic than gentamicin when perfused through the lateral canal in cats.[42] This study supported the choice to use streptomycin over gentamicin at the Shea Ear Clinic.

In the 1990s, Shea began using intratympanic perfusion with promising results. Because it had no risk of ototoxicity, he offered dexamethasone perfusion to many patients with MD early in the course of their treatment as an adjunct to medical therapy. He reported Class A or B control of vertigo in 76.7% and hearing worse in 6.3%. Patients who failed to improve were then offered perfusion with 120 mg/mL streptomycin plus 16 mg intravenous dexamethasone once daily for 3 consecutive days after being informed of the potential risk to hearing. This resulted in class A or B control of dizzy spells in 80.0% with hearing worse in 9.4%.[8] The protocol used in this report evolved from earlier studies at the Shea Ear Clinic, and the much lower concentration of 10 mg/mL streptomycin was eventually selected because it was found to be effective at relieving vertigo with very low rates of hearing loss.

There is disagreement about which dosing method and schedule is best to achieve vertigo control while minimizing hearing loss and about the optimal end point for therapy. Two meta-analyses of gentamicin studies have been published, and one of them examined this question. Chia et al. divided the studies into five types according to their dosing regimen (multiple daily, weekly, low dose, continuous, and titration) and compared their rates of complete and effective vertigo control, overall and profound hearing loss, and degree of vestibular ablation (complete or partial).[43] They found the titration method to have significantly better complete (81.7%) and effective (96.3%) vertigo control than others. The weekly method had the lowest rate of overall hearing loss (13.1%), and profound hearing loss was similar across groups. Degree of vestibular ablation was not a factor. In the other meta-analysis, Cohen-Kerem et al. found that 627 patients in 15 studies had complete (Class A) vertigo control in 74.7% and substantial (Class

TABLE III.
Quality-of-Life Scores for the Total, Global, Mental, Physical, Social, and Vertigo Domains..

QOL Domain	Pretreatment	Posttreatment	Mean Change	*P* Value
Total	28.5 ± 13.1	48.1 ± 14.8	19.6 ± 16.2	<.0001
Global	0.91 ± 0.80	2.42 ± 1.05	1.53 ± 1.30	<.0001
Mental	7.52 ± 3.83	9.80 ± 3.38	2.26 ± 3.59	<.0001
Physical	11.3 ± 5.86	21.5 ± 7.93	10.4 ± 8.29	<.0001
Social	8.50 ± 4.30	14.2 ± 4.16	5.65 ± 4.98	<.0001
Vertigo	2.51 ± 2.20	7.62 ± 3.15	5.30 ± 3.77	<.0001

QOL = quality of life.

TABLE IV.
Percentage of Patients Improved, Unchanged, or Worse After Streptomycin/Dexamethasone Inner Ear Perfusion in the Total, Global, Mental, Physical, Social, and Vertigo Subscore Domains.

QOL Domain	Improved, %	Unchanged, %	Worse, %
Total	90 ± 30	3 ± 17	7 ± 26
Global	88 ± 32	4 ± 20	8 ± 27
Mental	64 ± 48	24 ± 43	12 ± 32
Physical	90 ± 30	3 ± 17	7 ± 26
Social	84 ± 37	9 ± 29	7 ± 26
Vertigo	88 ± 32	11 ± 31	1 ± 10

QOL = quality of life.

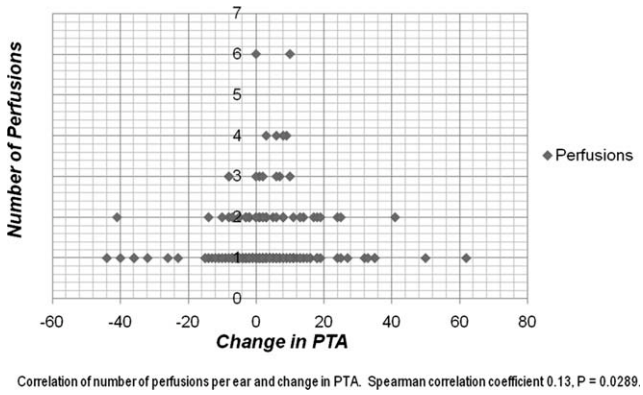

Fig. 2. Scatterplot of correlation between number of streptomycin/dexamethasone inner ear perfusion (SDIEP) treatments in a single ear and the change in pure tone average for that ear.

B) control in 92.7%.[44] They also found similar success rates of vertigo control between the studies but found that the titration regimens had a lower rate of hearing loss than fixed-dose regimens. The protocol used with SDIEP by this author is a hybrid between the fixed and the titration types, as a short fixed regimen is given to all patients initially and is then repeated only if and when symptoms return.

The advantage of this protocol over a weekly dosing schedule is that each SDIEP is given sufficient time to exert its effect and for any potential adverse effects to become apparent, which might take more than 1 week. Treatment is not stopped when vertigo control is adequate but rather is continued only when it is inadequate. Patients are told at the beginning that they will likely need one to three SDIEPs to adequately control their vertigo, and they may be spaced over months to years, depending on their response. Many of the patients in this study are still being followed, and some who had satisfactory vertigo control at the conclusion will eventually need additional SDIEPs. In this sense, the data are a "snapshot" of this group of patients, although it is large enough to demonstrate trends.

There are currently three general methods of intratympanic delivery: direct injection into the middle ear, round window sustained delivery via the IntraEar Microcatheter (Durect, Cupertino, CA), and the Silverstein MicroWick (Micromedics, St. Paul, MN). To date, none of them has proven superior to any other.[45] Because of this, Blakley advocates using the simplest method, direct injection through the tympanic membrane,[13] the route used at the Shea Ear Clinic. SDIEP is a "results-oriented" approach that is performed in an outpatient surgery center rather than the office to facilitate the three 2-hour periods that the patient lies with the ear up, which increases the time the perfusate is in contact with the round window membrane. A cost analysis of the use of a surgery center for SDIEP versus in-office treatment has not been performed but would have to examine the total number of treatments needed to achieve vertigo control as well.

Several factors highlight the difficulty associated with any analysis of intratympanic treatment. In this study, the average duration from SDIEP until follow-up audiogram was 94 days (range, 8–1,603 days), which is sufficiently long that the natural history of MD could be responsible for further deterioration in hearing in some patients.[46] In addition, there are inherent variables, like escape of perfusate through the eustachian tube and variation in the permeability of the round window membrane, that cannot be controlled. Other studies are concerned with the number of treatments necessary to reach an objective end point, but this author would argue that satisfactory control of dizzy spells is the only important end point. For this reason, the QOL survey did not ask about or attempt to correlate number of SDIEPs with results. After all SDIEPs necessary to control vertigo were completed, the rate of hearing loss (17.9%) was not much higher than the rate after a single procedure (15.7%).

The clinical effects of SDIEP on a typical hydropic ear seem to be a combination of reversible and irreversible ones. There is certainly some recovery after the initial insult to the labyrinth, but a small amount of permanent effect is usually observed. The transient disequilibrium, or "deafferentation syndrome,"[37] that many patients experience after aminoglycoside perfusion is not usually seen until 3 to 7 days later but almost always resolves within days to weeks. After this, most patients report significant improvement in vertigo and aural fullness, and less commonly in hearing and tinnitus, usually for a period of at least several months. How much of this effect with subablative doses of streptomycin is due to destruction of type I hair cells versus inhibition of dark cell function and endolymph production is unclear.[37] Patients will often have a lower summating potential—to—action potential ratio on the electrocochleogram following SDIEP as objective evidence of improvement in their hydrops. If they begin to have vertigo spells again after SDIEP, they are often less frequent and severe than before. Patients are continued on diuretics and a low-salt diet but usually require far less vestibular suppressants. The author's experience has been that when patients are experiencing "full-blown" attacks of vertigo, nausea, and vomiting, medical therapy alone is often inadequate to provide improvement in symptoms. SDIEP is used by the author in such cases early in the course of treatment and as a "maintenance plan" of sorts to control vertigo as needed in an ongoing fashion.

The hearing results from this study compare favorably with those from the meta-analysis by Chia et al., which found a 25.1% overall rate of hearing loss with intratympanic gentamicin. The lowest rate of hearing loss of any method in that review was 13.1%, with the weekly gentamicin protocol, only slightly lower than this author's rate of 15.7% with SDIEP. The average hearing loss in this study is lower than that of Cohen-Kerem et al., who reported deterioration in PTA of 1.5 dB and WRS of 2.0% in 549 patients from 15 reports on intratympanic gentamicin.

The MDOQ was mailed to all patients who had SDIEP by the author between July 2002 and May 2010, regardless of the number of treatments or the time

course over which they had them, because consistent information about vertigo control was not available for all patients. The survey allowed this group to be evaluated using a standardized set of criteria. There are a number disadvantages to this approach, however. Patients who had SDIEP years earlier have had MD longer and may have improved more through natural history[47] than a patient who had SDIEP recently or that may not yet have achieved adequate control of symptoms. Other weaknesses are the variability in time from SDIEP to post-treatment audiogram and selection bias from the back-to-back pairing of questions. To harness the validity of a proven instrument like the MDOQ and allow comparison with other treatment modalities, the author felt the survey should be used "as-is," without modification. The study was designed with these limitations in mind, in the hope that a sufficient number of SDIEPs would show meaningful trends.

CONCLUSION

SDIEP is safe for hearing, easy to perform, convenient for patients, and can be used to control vertigo in MD patients as an adjunct to a medical regimen. In this study, 78.9% of patients had adequate vertigo control after one SDIEP, 94.0% after two, and 98.0% after three. SDIEP compares favorably to other transtympanic aminoglycoside regimens in hearing preservation; 90% of patients experienced improvement in their QOL following SDIEP, and 88% experienced improvement in their vertigo. Transtympanic protocols like SDIEP have made more invasive procedures like endolymphatic sac surgery, vestibular nerve section, and surgical labyrinthectomy much less common in the treatment of MD.

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