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Chemical perfusion of the inner ear

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Perfusion of the middle ear using aminoglycosides for treatment of Meniere's disease was originally introduced by Schuknecht in the 1950s [1]. Perfusion of the inner ear using various medications has become a common form of treatment of inner ear disease [1–9]. In fact, intratympanic therapy to treat inner ear disease has demonstrated a rapid rise in popularity in recent years to become the most frequently utilized first-line treatment for the vertigo of Meniere's disease. The popularity of the technique can be attributed largely to several key advantages of placing medications directly into the inner ear: (1) the diseased ear is treated directly without affecting the entire body, (2) a higher concentration of medication can be obtained, and (3) systemic side effects of the drug are prevented. Additionally, the techniques are minimally invasive, can usually be performed in the office, are well accepted and tolerated by patients, and most otolaryngologists are comfortable performing the procedures.

Inner ear perfusion techniques vary from transtympanic blind injections to sustained release devices, including the Silverstein MicroWick (Micromedics, Eaton, MN) and the Round Window Microcatheter (Durect Corp., Cupertino, CA). The techniques have been utilized not only to treat the vertigo of Meniere's disease, but also to treat sudden sensorineural hearing loss (SSHL), autoimmune inner ear disease (AIED), tinnitus, and hearing loss associated with Meniere's disease. In this article, the various inner ear perfusion techniques utilized and the results obtained from these methods in treating inner ear disease are discussed.

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Historical perspective

Shortly after the drug was introduced, the ototoxic and vestibulotoxic effects of streptomycin were understood by 1948 [10]. Although Schuknecht [1] was the first to describe transtympanic utilization of aminoglycosides in the 1950s, he is also responsible for stimulating initial general interest in the use of streptomycin ablation for the treatment of Meniere's disease. In 1957, he reported on eight patients treated with transtympanic streptomycin for Meniere's disease [11]. Although all eight achieved chemical ablation of vestibular function, five lost all cochlear function. Over the ensuing decades, interest in North America was largely absent; however, in Western Europe, reports continued to emerge regarding the use of inner ear perfusion with aminoglycosides to treat vertigo [12,13].

Interest in North America was rekindled in the early 1990s with reports by Nedzelski et al [5,6]. Since that time, many investigators have reported on their results in treating Meniere's disease. The success rates achieved in controlling vertigo have been good, but side effects of significant ototoxicity with hearing loss have been observed on the order of 30% [14]. Many different perfusion techniques have been explored, including blind transtympanic injection, injection onto Gelfoam (Upjohn, Kalamazoo, MI) placed in the round window niche, use of the Round Window Microcatheter with continuous pump, and use of the Silverstein MicroWick [2,7,8,15,16]. Different forms of inner ear disease have also been treated with variable success.

Treatment concepts

It has been established that the primary route of entry of aminoglycosides into the inner ear is through the round window membrane [17]. Alternative routes include the annular ligament of the oval window, vasculature, and lymphatics [18]. After passing through the round window membrane, solute concentration has been noted to increase in the perilymphatic and endolymphatic spaces [19]. The elevated concentrations of the treating medications achieved in the inner ear fluids following perfusion are much higher than those concentrations achieved via systemic administration. The solute can diffuse throughout the cochlear and vestibular fluids, potentially causing effects on both cochlear and vestibular function.

Although medications can more selectively affect a particular population of inner ear cells (eg, vestibular hair cells), it is not possible at the present date to avoid having effects on the nontargeted cells. Thus, the potential for undesired side effects such as hearing loss is inherent. Some aminoglycosides are particularly cochleotoxic, such as amikacin and kanamycin, whereas others are primarily vestibulotoxic, such as streptomycin and gentamicin. In the treatment of vertigo, the goal is to capitalize on the vestibulotoxic effects of the perfused medication while avoiding the ototoxic effects. In theory, vestibular ablation eliminates the fluctuating afferent vestibular inputs to the brain experienced by patients with endolymphatic hydrops, thus eliminating recurrent vertigo episodes; however, initial postoperative and potentially chronic dysequilibrium can ensue. Bilateral procedures generally are not performed due to risk of complete vestibular ablation with associated oscillopsia and permanent imbalance.

When the entire middle ear space is diffusely perfused with aminoglycosides, it is unclear how much medication is applied directly to the round window membrane. Because the medications are topically applied, systemic absorption and associated side effects are largely avoided. The medication dissipates from the middle ear space by passing down the eustachian tube into the nasopharynx, eventually being swallowed. The medications used generally are not topically absorbed by the mucus membranes of the middle ear; however, the physician must be aware that the medication may achieve systemic concentrations if it passes down the eustachian tube and is absorbed by the gastrointestinal tract after swallowing (eg, dexamethasone).

In the treatment of vertigo of Meniere's disease, two primary philosophies exist: chemical ablation versus chemical alteration with gentamicin [20]. Chemical ablation has been highly successful in controlling vertigo but at the cost of increased risk of loss of cochlear function. Alternatively, chemical alteration potentially is less effective in controlling vertigo but has less chance of adversely affecting hearing. There are also two primary methods of time scheduling perfusions: fixed dosing versus titration. The technique patterned after Nedzelski et al [5,6] involves use of a predetermined fixed schedule of dosing of gentamicin in which a regular sequential pattern of perfusions is performed until the protocol is complete or adverse side effects are noted. More recently, authors have advocated use of titration techniques in which the dosing is titrated in order to achieve a specific end point, thus guiding conclusion of therapy. Repeated audiometric and vestibular testing is typically employed to guide the titration. Potential end points include objective measures on electronystagmography (ENG) testing. A goal utilized by the authors includes achievement of 100% reduced vestibular response (RVR) to both bithermal and ice-air caloric ENG testing without producing a hearing loss (an ablative but titrated technique; Silverstein et al [16]. In previous studies utilizing both fixed dosing regimens and titration protocols, vertigo control rates were similar, but a significantly higher level of hearing loss was noted in patients receiving fixed-dose perfusions [21].

Intratympanic steroids have also been utilized for treatment of several inner ear conditions, including Meniere's disease, SSHL, and AIED [16,22,23]. Because oral steroids are effective in treating these conditions, it seems logical that topical steroid perfusion could also be beneficial. In patients who fail oral steroid therapy, steroid perfusion remains a secondary option. For those patients in whom oral steroids are contraindicated, including those with diabetes, peptic ulcer disease, and immunosuppression, steroid perfusion is a viable alternative. Other medications may be potentially useful in the treatment of tinnitus, and the potentially higher perilymph/endolymph concentrations achieved with direct inner ear perfusion may make the technique superior.

Surgical techniques

Transtympanic injections

Many protocols exist for repeated transtympanic injections of gentamicin or steroids. In general, the patient is placed supine with the head turned toward the untreated ear. Anesthesia can be achieved with topical tetracaine solution mixed with alcohol and applied to the ear canal for ≥8 minutes [24], topical phenol applied to the posterior central portion of the tympanic membrane [25], and ear canal injection with 1% lidocaine with 1:100,000 epinephrine (buffered in 10% sodium bicarbonate to reduce stinging). The gentamicin or other treating solution is then injected into the middle ear space over the round window niche region (posteroinferior portion of the tympanic membrane) using a 1 mL tuberculin syringe with a long 25- or 27-gauge needle. A volume of approximately 0.3 to 0.5 mL is delivered until the middle ear is full of solution. Some authors advocate placement of a second hole in the tympanic membrane to allow escape of air. The patient is then instructed to lie with his head turned away from the operated side in the range of 15 to 45 minutes.

Others have utilized indwelling tympanostomy tubes to maintain a transtympanic route of delivery for repeated injections. Nedzelski et al [5,6] have utilized a myringotomy placed in the posteroinferior quadrant of the tympanic membrane. Then, a "T-type" ventilation tube with a butterfly catheter tubing attached is inserted for the duration of treatment. Medication is injected through the catheter to fill the middle ear space.

As part of the protocol of Nedzelski et al [5,6], the medicine is delivered once daily in the office and twice daily at home for 4 consecutive days. When the patient is seen on a daily basis, the patient is examined for nystagmus, deterioration in tandem gait, and worsening in bone conduction audiometry of >10 dB for three consecutive frequencies. Alternate titration protocols have the patient return on a biweekly to monthly basis [20]. Upon return, patients are questioned regarding changes in symptoms and evaluated with audiometry and ENG. These data are used to determine whether repeat treatment is warranted. When a ventilation tube is placed for the perfusions, it can be removed after therapy is complete.

Injection onto material in round window niche

These techniques utilize material placed in the round window niche in an attempt to provide a passive sustained release vehicle to deliver the medications. In this technique, the ear canal is anesthetized with local injections and a tympanostomy is created with a knife or laser. Otoendoscopy is performed with a 0° or 30° otoendoscope to ensure that the round window niche is free of obstruction (present in 20% of patients) [8]. If such obstructing mucosal bands or adhesions are present, they are gently removed with a small hook. Dry Gelfoam, 2×3 mm in size, is inserted against the round window membrane, and then the Gelfoam and middle ear space are saturated with 0.2 to 0.3 mL of solution. The patient remains with head tilted away for the predetermined time. Repeat injections can be performed before the Gelfoam dissipates, titrating, if desired, to symptomatology, ENG caloric testing, and hearing loss. Alternatively, material such as fibrin glue can be used [26]. The medicine (eg, gentamicin) is added to one of the two liquid components of the glue. The two components are mixed together in the round window niche, causing the glue to solidify. Medicine is presumably slowly released from the glue mass.

Microcatheter sustained delivery

Active sustained release techniques of delivery aim to provide near-continuous perfusion of the inner ear. The goal is to achieve relatively constant concentrations of medication within the inner ear fluids instead of periodic elevations in the concentrations followed by dissipation of solute, potentially to complete absence. It is felt that this technique may also help avoid spikes in the concentration that could be associated with toxic effects to the inner ear. The only sustained release delivery systems available that allow the physician and patient to control and alter delivery are the Round Window Microcatheter and the Silverstein MicroWick.

Placement of the round window membrane microcatheter typically requires the patient to be taken to a formal operating room and be placed under general anesthesia [2,27]. A tympanomeatal flap is elevated to expose the round window niche. Obstructing membranes are cleared from the round window niche. A microcatheter with an appropriately selected tip size (usually 1.5 or 2.0 mm in diameter) is gently inserted into the niche (Fig. 1). The bulbous and compressible tip locks in place into the bony niche. Special care is taken not to insert the tip too deeply and cause injury to the round window membrane. The catheter attached to the tip is primed with the medication of choice. The tympanomeatal flap is replaced over the catheter, and an expandable sponge is used to secure the catheter in the external ear. The catheter is connected to an electronic pump (Disetronics, Minneapolis, MN), and microdoses of the medication can be continuously pumped for a predetermined time period or titrated according to desired response. The microcatheter is removed in the clinic, and the tympanic membrane is allowed to heal.

MicroWick sustained delivery

Like the Round Window Microcatheter, the Silverstein MicroWick inner ear medication delivery technique provides direct and precise delivery of

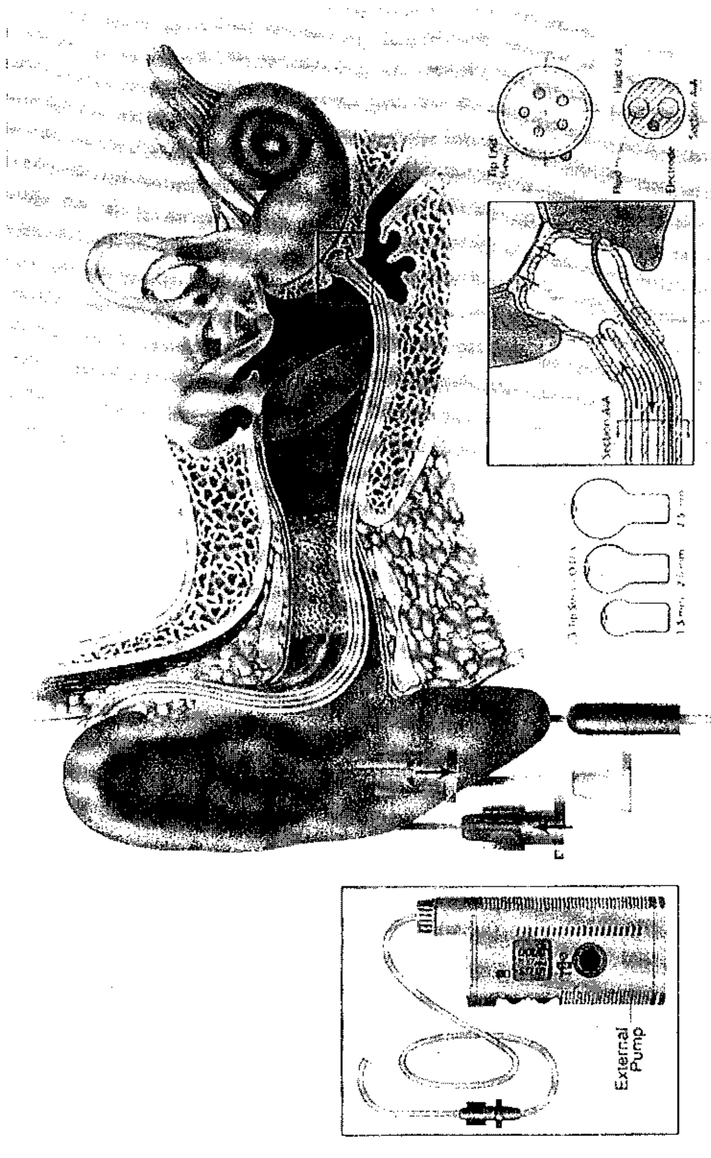

Fig. 1. Durect Round Window Microcatheter system, placed under a tympanomeatal flap and seated in the round window niche. The Disetronics pump, catheter tip sizes, close-up of the round window niche, and close-up of the catheter tip are displayed. (*From* Weisskopf P, Hoffer ME, Kopke RD, et al. Microdose gentamicin delivered via the Round Window Microcatheter: a therapeutic option in Meniere's disease. Oper Tech Otolaryngol Head Neck Surg 2001; 12:154–6; with permission.)

medication to the round window membrane [15,16,28]. It allows patient self-administration of the medication into the ear canal. The MicroWick absorbs the medication and transports it to the round window membrane where it perfuses directly into the inner ear fluids. This method is similar to the current concept of self-treatment for eye disease using medicated eye drops. The MicroWick is made from polyvinyl acetate and measures 1 mm in diameter by 9 mm long (Fig. 2). It is small enough to insert though a ventilation tube. The Silverstein silicone vent tube is 1.42 mm in diameter, with a 3.25 mm diameter flexible flange (Micromedics, Eaton, MN).

The procedure is performed in a noncertified office minor surgery room. The ear is anesthetized with local canal injections. A laser tympanostomy or vertical myringotomy is made over the round window niche. Usually, the round window niche can be seen through a normal tympanic membrane as a dark shadow beneath the tympanic membrane. When there is scarring of the tympanic membrane from previous infection, it can be difficult to determine visually the exact location of the round window beneath the tympanic membrane. The round window niche lies posterior (3.44 mm, SD $\pm$ 0.68 mm) and slightly inferior to the umbo of the malleus (113°, SD $\pm$ 9.8°) [29].

The middle ear is examined with an endoscope or the operating microscope to determine whether there are any obstructing membranes over the round window niche. When such membranes are present, a small pick is

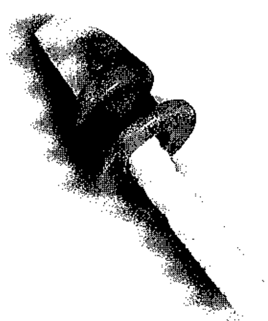

Fig. 2. Polyvinyl acetate MicroWick measures 1 mm in diameter by 9 mm long; the Silverstein silicone vent tube has a 1.42 mm diameter with a 3.25 mm diameter flexible flange. The two are shown as they would lie together after insertion through the tympanic membrane. (*From* Silverstein H, Jackson LE, Rosenberg SI. Silverstein MicroWick™ for the treatment of inner ear disease. Oper Tech Otolaryngol Head Neck Surg 2001;12:144–7; with permission.)

used to clear them. A ventilation tube is inserted into the tympanostomy opening and should allow direct visualization of the round window niche (Fig. 3). The MicroWick is then inserted through the tube and into the round window niche. The MicroWick and middle ear are saturated with the treating medication. The MicroWick will deliver a high concentration to the round window and allow perfusion into the inner ear fluids (Fig. 4). Patients continue to self-administer medication in the ear three times daily while lying for 15 minutes with the treated ear facing upward. Periodic testing (eg, weekly audiometric and vestibular testing) is performed to titrate the medication and determine when to discontinue therapy.

When the physician determines that therapy is complete, the MicroWick and tube are removed in one unit without the use of anesthesia. Placing either a right angle pick under the flange or cup forceps on the small tab, the vent tube is grabbed and removed with the MicroWick. The tympanostomy site may be patched with a 3 mm square piece of Gelfilm (Upjohn, Kalamazoo, MI) impregnated with antibiotic ointment. The tympanic membrane usually heals rapidly in 1 to 2 weeks, with or without the Gelfilm. If the MicroWick is left in place for an extended period of time (ie, over 6 weeks), the polyvinyl acetate may become adherent to the mucosa of the round window niche. This makes removing the MicroWick more difficult and can result (rarely) in the MicroWick breaking, leaving a piece of polyvinyl acetate in the middle ear. To correct this, the ear is injected with buffered lidocaine with adrenaline, and a pick is used to tease the MicroWick from the mucosa.

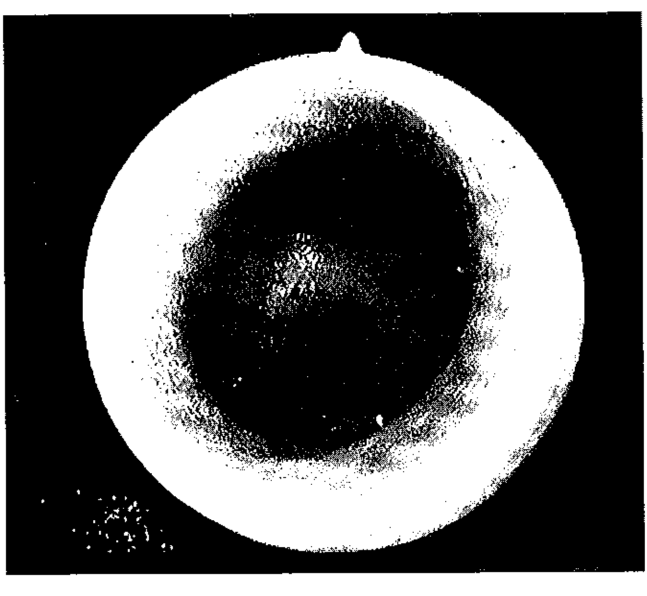

Fig. 3. Round window as seen through a ventilation tube in a left ear.

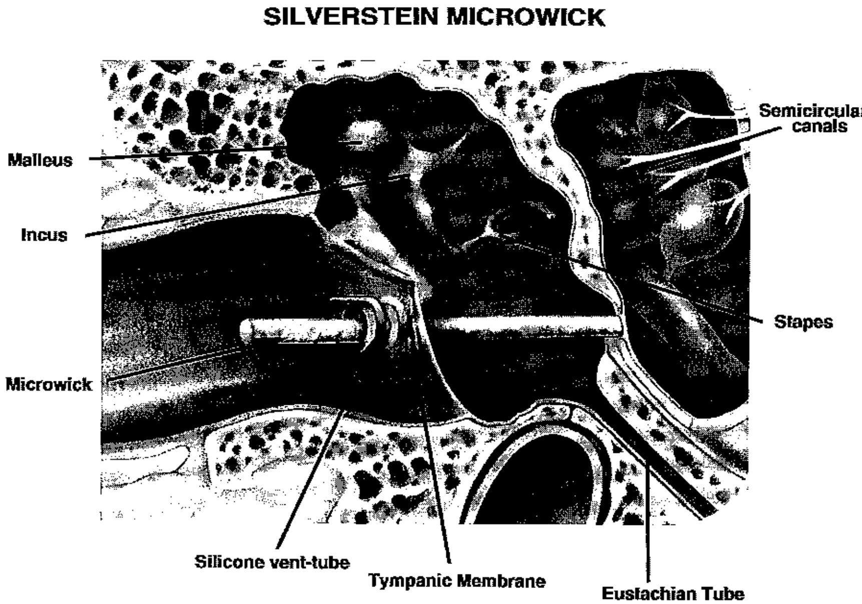

Fig. 4. Drawing depicting the MicroWick following placement, with the distal end lying against the round window membrane. The patient can self-administer medication to the proximal end for delivery. (*From* Silverstein H, Jackson LE, Rosenberg SI. Silverstein MicroWick™ for the treatment of inner ear disease. Oper Tech Otolaryngol Head Neck Surg 2001;12:144–7; with permission.)

Treatment of Meniere's disease with the MicroWick

In a compounding pharmacy, sterile techniques are used to prepare a 10 cc dilute solution of gentamicin otic solution. A concentration of 5 to 10 mg/cc (usually 10 mg/cc) is prepared from an intravenous vial of 40 mg/cc and then transferred into a sterile dropper bottle. The patient is instructed to lie in the supine position for 15 minutes with the treated ear facing upwards and to administer three drops of the medication into the ear canal three times daily. At the end of each week, testing is completed consisting of audiometric air, bone, and discrimination scores, electrocochleography, and balance function by warm-air and ice-air caloric ENG. Patients are also questioned regarding changes in their subjective symptoms of vertigo, aural pressure, tinnitus, and imbalance. Depending on the objective test results and the patient's symptoms, treatment is either continued or discontinued. The goal of this treatment is to obtain a 100% RVR to both bithermal and ice-air caloric ENG testing without producing a hearing loss. When this is achieved, therapy is discontinued. The usual length of treatment is 2 to 3 weeks (range 1–6 weeks). If a 100% RVR is not achieved and the vestibular function remains stable after several weeks of treatment, then the treatment is discontinued.

More recently, if the hearing significantly decreases during the treatment period (worsening of ≥10 dB pure tone average (PTA) or ≥15% speech discrimination), then a steroid rescue of hearing protocol is initiated. Prednisone, 60 mg/d for 2 weeks, followed by a taper is prescribed. Gentamicin may or may not be continued with the hearing loss, depending on severity. Initial results are very encouraging and have shown a significant recovery of hearing with steroid treatment [30].

Treatment of sudden deafness and AIED with the MicroWick

Oral steroids are frequently employed in the treatment of SSHL and AIED. Patients who can tolerate systemic steroids are initially treated with oral steroids first. If patients do not fully respond after 2 weeks of oral steroids, then inner ear perfusion with dexamethasone via the MicroWick is a secondary option. Patients who have a medical contraindication to steroids such as diabetes, hypertension, or peptic ulcer disease can be treated primarily with direct inner ear perfusion while avoiding the systemic effects of the drug.

A solution of dexamethasone 4 to 24 mg/cc is prepared at a compounding pharmacy and placed in a sterile dropper bottle. Lower doses (ie, 4 mg/cc) produces less chance of tympanic membrane perforation. The patient is given instructions to lie in the supine position with the head turned for 15 minutes and to instill three drops three times daily. In addition, antibiotic eardrops are applied once daily to prevent infection. Hearing is measured after 2 weeks; if hearing is responding but is still not completely recovered, then the dexamethasone perfusion may be continued for another 2 weeks before removing the MicroWick.

Results

Transtympanic injections for Meniere's disease

Vertigo control rates with transtympanic therapy for Meniere's disease generally have been good. Blakely [14] reviewed 18 articles reporting the results of transtympanic gentamicin. Vertigo control success rates ranged from 77% to 100%. Hearing loss was cited to occur in the range of 0% to 75%, largely depending on the treatment philosophy: vestibular ablation versus alteration. The concentration of the gentamicin and the injection protocol utilized appeared to have minimal effect. The approximate mean hearing loss observed was on the order of 30%.

Transtympanic injections for sudden deafness and AIED

In the earliest study (to the authors' knowledge) utilizing transtympanic corticosteroids for the treatment of SSHL, 38% had at least a partial response [31]. Parnes et al [32] reported that 54% of their patients treated within 6 weeks of the onset of SSHL had a significant recovery of hearing

Microcatheter for Meniere's disease

Few studies have reported on the results of the Round Window Microcatheter. DeCicco et al [2] reported on 18 patients treated for Meniere's disease. With follow-up of 6 to 8 months, vertigo was eliminated in all patients. Additionally, tinnitus was improved in 83%, and aural fullness was relieved in 94%. Hearing loss was observed in only one patient (5.6%).

Microcatheter for sudden deafness and AIED

Kopke et al [27] reported on a small series of patients treated for SSHL with the Round Window Microcatheter. Of the six patients treated within 6 weeks of onset, five improved their speech discrimination. In the three treated more than 6 weeks after the onset of the SSHL, no significant improvement was noted.

MicroWick for Meniere's disease

Patient acceptance of the procedure has been excellent. During an 18-month period, 92 patients were treated for Meniere's disease with the MicroWick procedure and gentamicin inner ear perfusion [16]. Of those responding to a questionnaire, 85% had relief of vertigo, 67% had improvement or relief of ear pressure, and 57% had improvement or relief of tinnitus. Only seven patients (8%) needed further treatment for Meniere's disease. Of the 81 patients with complete ENG data, 77% of patients achieved 100% RVR with warm-air caloric testing after treatment with the MicroWick and dilute gentamicin. Forty-one percent of patients achieved 100% RVR with ice-air caloric ENG.

When the hearing results were evaluated using the 1995 American Academy of Otolaryngology–Head and Neck Surgery Committee on Hearing and Equilibrium criteria [33] regarding Meniere's disease (ie, worsening of $\geq$10 dB PTA or $\geq$15% speech discrimination representing a significant hearing loss), the overall incidence of hearing loss was 36%. In those with pretreatment functional hearing (PTA $\leq$ 50 dB), the PTA remained the same or improved in 69%, and the discrimination score remained the same or improved in 77%. Of those with functional hearing who experienced hearing loss, the average drop was 9 dB PTA and 9% discrimination. Most patients who experienced increased hearing loss did not complain of their change in hearing and were pleased to be relieved of their vertigo attacks.

When significant changes in PTA or speech discrimination are observed during gentamicin perfusion, the authors presently utilize an oral prednisone rescue of hearing. In 12 patients experiencing significant drops in hearing, 9 (66.6%) experienced recovery of hearing to pretreatment levels [30]. Use of steroids did not adversely effect objective changes in the RVR. Oral steroid preservation of hearing, where steroids are started simultaneously with the gentamicin perfusion, also appears promising.

The authors previously have tried other protocols to deliver the gentamicin to the inner ear, including transtympanic gentamicin injections and injecting gentamicin onto Gelfoam in the round window niche. It is interesting to compare results of the MicroWick with the earlier protocol of injecting gentamicin, 27 mg/cc, onto Gelfoam placed in the round window niche with 5 days separation between the two injections (Table 1) [8,16]. There is a statistical difference between the groups regarding vestibular function. One hundred percent warm-air caloric RVR was obtained in 36% of the group treated 5 days apart compared with 78% in the MicroWick group. For ice-air caloric testing, in the group treated 5 days apart, only 9% obtained a 100% RVR compared with 43% of the MicroWick group. Thus, the MicroWick technique resulted in a more effective ablation of the vestibular system than did repeated injections of gentamicin onto material in the round window niche.

MicroWick for sudden deafness and AIED

Nineteen patients were treated with dexamethasone perfusion for SSHL [16]. Five of the patients (31%) had a positive response. The average gain in hearing was 45 dB PTA and 39% discrimination. Patients treated early in the disease had better results, although one patient had a good response after more than 1 year following onset of the hearing loss. Only three patients were treated for AIED, and the results were inconclusive.

Complications

Serious complications are rarely seen with intratympanic therapy. Although each method of delivery has potential associated complications, certain complications and side effects are inherent to all delivery techniques. A common and very concerning side effect seen with gentamicin inner ear perfusion is hearing loss. Temporary dysequilibrium occurs very frequently, but prolonged and severe unsteadiness is rare. These problems are treated with vestibular rehabilitation therapy. It is difficult to predict which patients will have difficulty with imbalance during and after the treatment; however, if a patient has chronic dysequilibrium before treatment, then the possibility

Table 1
Vestibular function comparison following treatment with the MicroWick and dilute gentamicin versus gentamicin injected onto Gelfoam placed on the round window membrane

Treatment	No. patients	Bithermal 100% RVR	Ice 100% RVR	Bithermal mean RVR	Ice mean RVR
MicroWick and dilute gentamicin (10 mg/cc)	80	78%	43%	88%	66%
Gentamicin (27 mg/cc) injection onto Gelfoam	22	36%	9%	62%	37%

Abbreviation: RVR, reduced vestibular response.

of further imbalance should be explained to the patient. Persistent tympanic membrane perforations can occur with therapy, particularly in patients treated with dexamethasone perfusion. In fact, this problem has prompted the authors to change their dexamethasone concentration from 24 mg/cc to 4 mg/cc in hopes of reducing the steroid effect of poor healing on the edges of the tympanostomy sites. These perforations can usually be repaired in the office by fat myringoplasty.

Summary

In general, chemical perfusion therapy of inner ear disease is safe, inexpensive, and easy to perform. High inner ear medication concentrations can be achieved while minimizing systemic side effects. Most delivery methods are minimally invasive and can be performed in the office. The treatment is usually well accepted by patients. Vertigo control rates for Meniere's disease have been excellent—rivaling other prominent surgical treatments—allowing intratympanic therapy to become the most prominent first-line treatment for Meniere's disease. Side effects of ototoxicity occurring in approximately 30% of patients remain as one of the primary hurdles to overcome. Most patients who experience hearing loss, however, do not complain of the loss and are simply happy to be free of their vertigo attacks. The use of oral steroids to rescue and preserve hearing during gentamicin perfusion remains promising, and complete recovery and even hearing improvement have been observed [30]. Steroid perfusion of the inner ear also is variably effective for the treatment of SSHL, and is particularly indicated when oral steroids fail or are contraindicated due to other health reasons.

Many inner ear perfusion methods and philosophies of treatment exist. Each technique has its associated advantages and disadvantages, and the individual surgeon must decide which technique to use in concordance with the patient's disease and expectations. In the future, new medications likely will be developed to treat certain types of inner ear disease, including SSHL, tinnitus, and various forms of vertigo. These medications can be administered by direct chemical perfusion of the inner ear.

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