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Targeted Topical Steroid Therapy in Sudden Sensorineural Hearing Loss

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Objective: To treat patients with sudden sensorineural hearing loss (SSNL) who failed oral prednisone therapy by using a round window membrane (RWM) microcatheter. This topical delivery strategy sought to improve effectiveness of steroid treatment to the inner ear by targeting drug delivery to the RWM.
Study Design: Nonrandomized prospective design.
Setting: Tertiary care facility.
Patients: Six patients with severe unilateral SSHL, five of whom were refractory to a course of oral steroid therapy treated within 6 weeks of SSHL and three additional patients treated more than 6 weeks after SSHL.
Intervention: Therapeutic use of RWM catheter.
Main Outcome Measures: Pure-tone averages (PTAs) and word identification scores (WIS).
Results: Five of the six patients treated within 6 weeks of SSHL improved their WIS. Of the six, four returned to baseline hearing, one recovered hearing that could benefit by hearing amplification, and one regained moderate improvement in PTA but not WIS.
Conclusion: Targeted topical steroid administration avoids the significant systemic side effects of oral steroids and may offer more effective dosing than simple transtympanic injection of medicine. Although these findings are preliminary, it is possible that after further study, targeted drug delivery may be a useful technique to consider in patients with severe to profound hearing loss that have failed all other management options. **Key Words:** Topical steroids—Sudden sensorineural hearing loss.
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Sudden sensorineural hearing loss (SSHL), commonly described as an abrupt onset of hearing loss, is reported to occur in 5 to 20 per 100,000 population (1). Spontaneous recovery (without therapy) varies from 30% to 60%, most often resolving within 2 weeks after onset (2–4). High-dose systemic steroid therapy improves hearing recovery; however, persistent hearing losses after 2 weeks of oral steroids have a poorer prognosis (5,6). Transtympanic steroid therapy for chronically progressive hearing loss as well as SSHL has been reported with partial success (7,8).

Our earlier experiments demonstrated controlled administration and uptake of medicine in an animal model. More recently, our studies have used an active sustained release device to treat patients with Ménière's disease using gentamicin (9,10). Our animal and human data have demonstrated different uptake kinetics with different effects on patients when gentamicin was administered via the round window microcatheter (a sustained release device developed by IntraEar, Inc., Denver, Colorado, USA) compared with a simple transtympanic administration of gentamicin (9,10). Because of our previous success with this device, we began administration of steroids using the microcatheter in patients with significant SSHL in whom oral steroid administration had failed. This strategy was an attempt to improve the effectiveness of steroid treatment to the inner ear by enhancing the coupling of drug delivery to the round window membrane.

MATERIALS AND METHODS

Subjects

Patients who came to our institution between July 1998 and April 1999 with reports of SSHL (hearing loss on awakening or having developed over 72 hours or less) and who did not respond to 2 weeks of oral steroid therapy were included in the study. All individuals underwent a standard evaluation, including an otolaryngologic history and physical, a routine audiologic test battery, syphilis serology, erythrocyte sedimentation rate, antinuclear antibody testing, rheumatoid factor testing, and magnetic resonance imaging to rule out retrocochlear pathology. The patients were initially treated with prednisone (60 mg by mouth every morning or 20 mg by mouth three times a day). Before catheter placement, patients were informed that this was a new treatment and were counseled regarding the risks of otologic surgery and further hearing loss and dizziness.

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The two treatment groups in this study were divided by the period from onset of hearing loss until the time of catheter placement. Individuals who underwent catheter placement 6 weeks or less from the onset of hearing loss constituted the early group, and patients receiving catheter placement 7 weeks or longer after hearing loss constituted the late group.

The early group was composed of six individuals. Four of the individuals in this group experienced idiopathic SSHL that did not respond to a 2-week trial of oral steroid. One patient reported a sudden sensorineural loss 4 weeks after a stapedotomy (initially the patient had had an improvement in hearing because of a reduced air-bone gap from the surgery, but had a SSHL 4 weeks after surgery). Middle ear exploration did not reveal a reason for the sudden hearing loss. The final patient was undergoing aminoglycoside treatment for Ménière's disease and experienced a sudden sensorineural hearing loss. She was given oral steroid therapy while the gentamicin in the catheter was removed and microcatheter instillation of methylprednisolone was initiated. Oral steroid administration was stopped after 1 day in this patient.

The late group was composed of three individuals with SSHL: one in whom the condition was idiopathic, a second who sustained a SSHL after exposure to a loud noise, and a third who acquired SSHL after being struck in the side of the head by a golf ball.

Microcatheter treatment

With the patient under general anesthesia, a modified tympanomeatal flap was elevated to expose the round window niche. After clearing the round window niche of any false membranes or adhesions, a microcatheter with an appropriately sized tip (usually 1.5 or 2.0 mm in diameter) was gently inserted into the bony niche. The tip is bulbous and compressible and locks into place in the bony opening of the niche. Care was taken so as not to insert the catheter too deeply into the niche to avoid possible injury to the round window membrane. The catheter was preloaded with 0.125 mL of methylprednisolone (Solu-Medrol, methylprednisolone sodium succinate, Pharmacia & Upjohn, 62.5 mg/mL) at the time of surgery. After surgery, methylprednisolone (62.5 mg/mL) was continuously pumped for 14 days into the catheter at a rate of 10 μL/hour using an electronic pump (Disetronics, Inc., Minneapolis, MN, USA).

Routine audiometric bone and air conduction pure tone thresholds were obtained using Grason Stadler Instruments (GSI 16 or 10; Milford, NH, U.S.A.) audiometers before, during, and after catheter placement as well as at several follow-up examinations. Standard speech audiometry was administered to determine a percentage word identification score (0%–100%) using the Massachusetts Eye and Ear 25-word list, presented live-voice at 40 dB SL re: SRT. Middle ear function was assessed with a GSI-33 middle ear analyzer (version 2) for tympanograms, physical canal volumes, and acoustic reflex thresholds.

Hearing improvement

Hearing improvement was defined as a decrease in the four-frequency (0.5, 1, 2, and 3 kHz) pure tone average (PTA) of 10 decibels or more, or an increase in word identification score (WIS) of 15% or more.

Statistical analysis

All statistical analysis was conducted using a standard statistical software package (Microsoft Excel version 4.0) and STATA statistical software version 4.0 (STATA Corp., College Station, TX, U.S.A.). The mean four-frequency PTA and before and after in situ treatment of the early treatment group were analyzed using a Wilcoxon signed rank test. Mean WISs were compared before and after in situ treatment with a paired t test for means. Significance was determined to be at the level of $p < 0.05$. Statistical testing was not performed on the late treatment group because of the small number of patients. Their data will be presented descriptively as individual case data profiles.

RESULTS

As shown in Table 1, all individuals in the early group had severe to profound hearing loss before in situ steroid treatment, with a mean PTA in the affected ear of 93.3 dB or mean WIS of 1.3%. All individuals in the early group demonstrated an improvement in PTA after microcatheter treatment. Five of the six patients improved their WIS, and four (two of the idiopathic patients, the poststapedotomy patient, and the aminoglycoside patient) returned to pre–hearing loss PTA. Of the six patients in the early group, four returned to normal hearing, one recovered hearing that could be benefited by hearing amplification, and the last regained moderate improvement in PTA but not WIS.

Early group four-frequency PTAs are shown for individual and group means after the microcatheter treatment in Figures 1 and 2, respectively. As can be seen in Figure 2, the PTA in this group showed a marked improvement from 93.2 to 42.5 dB HL (Wilcoxon signed rank for

TABLE 1. *Functional assessments of SSHL patients treated within 6 weeks of hearing loss (early treatment group)*

M/F	Age (yrs.)	SSHL etiology	Baseline PTA	Pre-Rx PTA	Post-Rx PTA	Baseline WIS	Pre-Rx WIS	Post-Rx WIS	AC	Time from SSHL to microcatheter
F	16	Poststapes	65.0	107.5	63.5	100	0.0	75.0	F	4 wk
F	51	Idiopathic	10.0	75.0	7.5	100	4.0	100.0	F	4 wk
M	59	Idiopathic	NA	68.8	42.5	NA	4.0	54.0	DS	6 wk
F	48	Idiopathic	NA	115.0	60.0	NA	0.0	0.0	F	4 wk
F	61	Gentamicin	45.0	115.0	51.3	76.0	0.0	48.0	DS	24 hr
M	48	Idiopathic	35.0	78.8	30.0	96.0	0.0	96.0	F	4 wk
Avg.	47.2			93.3	42.5		1.3	62.2		
STD	16.2			21.41	21.05		2.31	37.1		
SEM				8.74	8.59		1.15	15.3		

SSHL, sudden sensorineural hearing loss; M/F, male or female; PTA, pure tone average is the average of 0.5-, 1.0-, 2.0-, and 3.0-kHz hearing levels in dB HL; STD, standard deviation; SEM, standard error of the mean; WIS, word identification score (%); NA, not available; AC, audiometric configuration where F = flat and DS = descending slope.

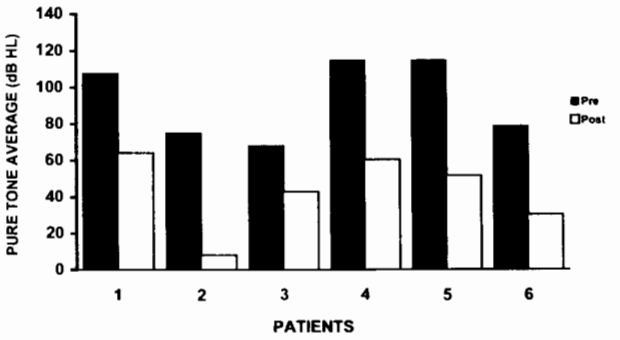

FIG. 1. Individual pure-tone average for patients (n = 6) in the early group before and after in situ steroid treatment. Patients in the early group lost their hearing less than 6 weeks before microcatheter steroid treatment and failed to respond to oral steroids.

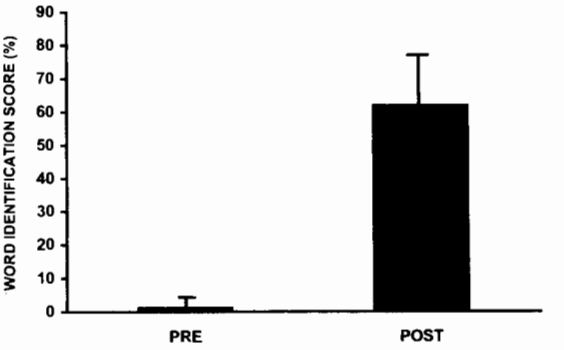

FIG. 3. Mean word identification score for the early group (n = 6) before and after microcatheter infusion therapy. The word identification score improved from a mean ± SEM of 2 ± 1.15% to 62.2 ± 15.3% ($p < 0.01$).

treatment effect, $p < 0.03$). In Figure 3, the mean WIS is depicted for the early group before and after microcatheter infusion therapy. The WIS improved from an average of 1.3 to an average level of 62.2% ($p < 0.01$).

There was no improvement of either PTA or WIS for any of the patients in the late group between the preoperative and postoperative in situ treatments. Individual PTA values are given in Table 2. One patient (the individual struck with a golf ball) had a further loss of hearing accompanied by vertigo 12 hours after catheter placement. In this patient, no evidence of a perilymph fistula was found either on initial catheter placement or on removal of the catheter shortly after the onset of symptoms.

At present, all patients in both groups are at 2 to 12 months after microcatheter treatment and have maintained their hearing levels on their most current audiograms (early group, 2–12 months, average 6.7 months; late group 7–11 months, average 9.7 months).

DISCUSSION

Of the many causes of hearing loss, SSHL is the least understood. Although an exact definition does not exist clinically, most authors agree that SSHL can develop in 72 hours or less or that it can occur on wakening in the morning (1,2). All patients in the early group had hearing loss that occurred over 24 hours or went to bed with no perceived hearing loss and awoke with near-total deafness in one ear. Several possible causes of idiopathic SSHL have been suggested, including vascular lesions, membrane breaks, and viral lesions (1). The temporal bone collection at the Massachusetts Eye and Ear Infirmary contains specimens of individuals with SSHL. These specimens demonstrate a variety of findings that are similar to those seen after cases of mumps and rubella and dissimilar from the fibrosis and osteoneogenesis seen with vascular disorders (11). Seltzer and Mark demonstrated inflammatory findings on magnetic resonance imaging during active sudden hearing loss, which disappeared as symptoms resolved, further suggesting a viral/inflammatory cause of this disorder (12). However, the most common classification for SSHL is idiopathic (1). There was a similar finding in our study, in which the majority of patients (56%) had idiopathic SSHL.

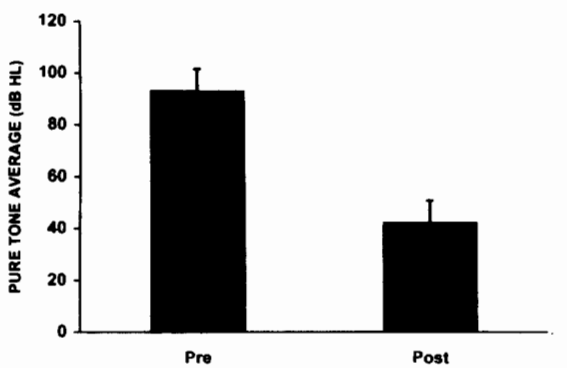

FIG. 2. Pure-tone average for the early group (n = 6) before and after in situ steroid therapy. In situ steroid infusion significantly ($p < 0.03$) reduced pure-tone average from a mean ± SEM of 93.31 ± 8.74 to 42.5 ± 8.59 dB HL, respectively.

Many investigators have attempted to determine prognostic variables for SSHL. Fetterman et al. examined 837 cases of idiopathic SSHL and found a significant correlation between the severity of the initial hearing loss and the time to initial treatment (13). In that study, those who were treated more than a month after the initial hearing loss had a poorer chance for improvement. Hughes et al. examined a group of patients with SSHL and added a response within 2 weeks as an additional prognostic variable (1). The most common treatment is high-dose oral steroid therapy, with a reported success rate of 78% in all patients with SSHL (5). However, the improvement rate is much less than in patients whose hearing loss was similar to that in our patients. Byl (2) reported that patients who were seen later than 7 days after severe or profound hearing loss had a 15% to 20% chance of complete recovery. Additionally, Saeki and Kitahara reported that only 24% of SSHL patients showing no improvement in hearing in the first 14 days exhibited any significant long-term progress (4). Our early patients (with one exception, the Ménière's disease patient) had experienced more than 4 weeks of hearing loss and had not responded to 14 days of oral steroid

TABLE 2. *Functional assessments of SSHL patients treated after 6 weeks of hearing loss (late treatment group)*

M/F	Age (yr)	SSHL etiology	Baseline PTA	Pre-Rx PTA	Post-Rx PTA	Baseline WIS	Pre-Rx WIS	Post-Rx WIS	AC	Time from HL to microcatheter (wk)
M	69	Trauma		51.0	115.0		64.0	0.0	DS	7
M	61	Noise		45.0	50.0		84.0	74.0	DS	10
F	56	Idiopathic		115.0	115.0		0.0	0.0	F	>10
Avg.	62.0			70.4	96.7		48.0	24.7		
STD	6.56			38.7	31.8		42.3	42.7		

SSHL, sensorineural hearing loss; PTA, pure tone average is the average of 0.5-, 1.0-, 2.0-, and 3.0-kHz hearing levels in dB HL; STD, standard deviation; SEM, standard error of the mean; WIS, word identification score (%); NA, not available; AC, audiometric configuration where F = flat and DS = descending slope.

therapy before the catheter placement. For those who did not achieve complete recovery, it is plausible that earlier treatment with microcatheter steroids might have resulted in a greater degree of improvement. Indeed, in the patients with long-standing hearing loss, microcatheter administration of steroids had no benefit. Interestingly, those individuals with the greatest degree of recovery began showing hearing improvement within 48 hours of microcatheter placement. Those showing no changes within 48 to 96 hours either had less improvement in hearing or, as in the case of all the late patients, demonstrated no amelioration.

Over the past decade, the combination of basic science and clinical studies has led to the development of transtympanic corticosteroid treatment of some hearing disorders. A well-designed study by Shirwany et al. demonstrated that transtympanic corticosteroid in guinea pigs caused no morphologic or functional disturbance in the ear (14). Parnes et al. reported in an experimental animal model that corticosteroids administered to the middle ear were able to achieve higher inner ear concentrations than when administered systemically (7). This was especially true for methylprednisolone. Silverstein et al. reported that approximately 38% of patients with idiopathic SSHL or SSHL from other causes who were treated with transtympanic corticosteroids had at least a partial response (8). Subsequently, Parnes et al. reported that 7 of 13 (54%) of their SSHL patients who were treated with transtympanic corticosteroid within 6 weeks of onset of hearing loss made a significant recovery of hearing thresholds (7). Transtympanic corticosteroid treatment, however, has potential limitations, namely a lack of precise coupling to the round window membrane with loss of drug down the eustachian tube and potential blockade by pseudomembranes in the round window niche. Delivery of the corticosteroid to the round window membrane with enhanced coupling, using a catheter inserted in the niche where pseudomembranes are removed surgically, is a logical next step in enhancing steroid treatment of the inner ear.

Although no direct proof exists that our patients' hearing recovery was attributable to the microcatheter administration of steroids, evidence suggests that there is a potential therapeutic window during which injured sensory cells or neurons can be rescued (15,16). The principal known effects of methylprednisolone are antiinflammatory and neuroprotective (17). Antioxidant (18–21) and antiapoptotic effects for this agent have also been reported (22,23). Thus, the benefits realized in these patients may have resulted from a variety of mechanisms. More basic science needs to be done to ascertain the exact mechanisms of action of corticosteroids in the inner ear.

The complete hearing loss and dizziness cannot be explained for the one patient in the late group. Given that he had experienced a traumatic event (golf ball to the head), the possibility of a pretreatment perilymph fistula could be entertained, but no fistula was seen at the time of microcatheter placement, nor was the patient dizzy before surgery. The patient initially did well postoperatively and experienced hearing loss and dizziness 12 hours after surgery. Upon removal of the microcatheter, no perilymph fistula was seen. The patient's vertigo converted to disequilibrium 3 days later, and this disequilibrium resolved after 4 weeks of vestibular rehabilitation. It appears that the patient had labyrinthitis. It cannot be determined whether the steroid caused this labyrinthitis or whether the labyrinthitis was purely coincidental with the treatment. A review of the last 20 years of English literature revealed no other reported cases of SSHL attributed to transtympanic steroid. Other compounds in the methylprednisolone solution may have affected the inner ear in this patient. However, all patients were administered a solution identical to what this patient was given without experiencing dizziness or hearing loss. The cause and mechanism of hearing loss could not be completely ascertained in this patient or for several of the other patients. It is possible that methylprednisolone might be helpful for some causes of SSHL and harmful for others. Finally, this patient's hearing loss may represent a dose-response effect, where doses higher than some therapeutic level may be harmful. For all these reasons, we are using this treatment only for patients with severe to profound hearing loss in whom more conservative therapy has failed, and we suggest the same precaution for other clinicians until definitive answers to these questions can be obtained.

We believe that targeted topical steroid administration may offer several advantages over systemic or transtympanic injection. This mode of delivery avoids the significant systemic side effects that can be associated with oral administration of steroid. It also offers more effective dosing than simple injection of the medicine across the eardrum. In fact, by avoiding such systemic side effects

as adrenal suppression and aseptic necrosis of the hip, this method may actually be safer than systemic administration of the medicine.

Another possible reason for the effectiveness of targeted delivery is that a higher steroid level in the cochlear neurosensory tissue may be achievable compared with oral or even transtympanic injection (7). This may allow for an effect that would not be seen with systemic or transtympanic administration. Different medicines can be added to the catheter, or the pump rate could be changed without any added discomfort for the patient, as would be necessary for repeated transtympanic injections. The pH of the steroid solution can be quite uncomfortable for some patients undergoing transtympanic injection (13) because of the volume needed, whereas with targeted delivery administration, the lower volume is less likely to cause discomfort. Many patients would prefer a single operative procedure to repeated injections.

Potential disadvantages may include the risk and expense of general anesthesia and operating room time. In addition, a small tympanic membrane perforation is possible after this procedure. In our series of nine patients, there were three small perforations. One short-term patient required paper patch, the second short-term patient opted for no therapy, and a long-term patient opted for an underlay tympanoplasty. We believe it important to warn patients about the possibility of a perforation, which may require another operation to repair. We also warn all patients about the possibilities of substantial worsening of hearing in the treated ear and transient vertigo.

To address this question and more fully study this treatment, our group is beginning a prospective randomized trial examining the efficacy of this treatment of severe to profound SSHL. It remains to be demonstrated whether this modality will confer a significant therapeutic advantage over oral or transtympanic steroid delivery.

SUMMARY

We have reported hearing recovery after microcatheter administration of methylprednisolone in patients with severe to profound SSHL from a variety of causes. Presently, it cannot be directly ascertained that microcatheter delivery of steroids resulted in hearing improvement. However, considering our patients' duration of hearing loss, which was more than 4 weeks, and also considering that oral steroids had been unsuccessful in five of the six patients, it is suggestive that the strategy had some effect. It is our belief that this information is important to practitioners, because this modality may someday represent a reasonable treatment option for patients with severe to profound hearing loss in whom oral steroids have been unsuccessful. While promising, this method of therapy needs further study in controlled prospective trials. Because of the potential risk of additional hearing loss, this procedure is not recommended for individuals with moderate hearing loss or serviceable hearing such as with a hearing aid. In addition, we have found no benefit in patients who are implanted with the catheter more than 6 weeks after the onset of hearing loss. Finally, it is important that both basic science and well-controlled clinical trials continue to document the most appropriate use and timing of this treatment modality in the emerging field of inner ear medicine delivery.

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