

Oral vs Intratympanic Corticosteroid Therapy for Idiopathic Sudden Sensorineural Hearing Loss

A Randomized Trial

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IDIOPATHIC SUDDEN SENSORINEURAL hearing loss, an unexplained unilateral sensorineural hearing loss with onset in less than 72 hours, has an estimated incidence between 5 and 20 per 100 000 persons per year.¹ This is likely to be an underestimate because many who recover quickly never seek medical attention.² Several large case series, including a

Context Idiopathic sudden sensorineural hearing loss has been treated with oral corticosteroids for more than 30 years. Recently, many patients' symptoms have been managed with intratympanic steroid therapy. No satisfactory comparative effectiveness study to support this practice exists.

Objective To compare the effectiveness of oral vs intratympanic steroid to treat sudden sensorineural hearing loss.

Design, Setting, and Patients Prospective, randomized, noninferiority trial involving 250 patients with unilateral sensorineural hearing loss presenting within 14 days of onset of 50 dB or higher of pure tone average (PTA) hearing threshold. The study was conducted from December 2004 through October 2009 at 16 academic community-based otology practices. Participants were followed up for 6 months.

Intervention One hundred twenty-one patients received either 60 mg/d of oral prednisone for 14 days with a 5-day taper and 129 patients received 4 doses over 14 days of 40 mg/mL of methylprednisolone injected into the middle ear.

Main Outcome Measures Primary end point was change in hearing at 2 months after treatment. Noninferiority was defined as less than a 10-dB difference in hearing outcome between treatments.

Results In the oral prednisone group, PTA improved by 30.7 dB compared with a 28.7-dB improvement in the intratympanic treatment group. Mean pure tone average at 2 months was 56.0 for the oral steroid treatment group and 57.6 dB for the intratympanic treatment group. Recovery of hearing on oral treatment at 2 months by intention-to-treat analysis was 2.0 dB greater than intratympanic treatment (95.21% upper confidence interval, 6.6 dB). Per-protocol analysis confirmed the intention-to-treat result. Thus, the hypothesis of inferiority of intratympanic methylprednisolone to oral prednisone for primary treatment of sudden sensorineural hearing loss was rejected.

Conclusion Among patients with idiopathic sudden sensorineural hearing loss, hearing level 2 months after treatment showed that intratympanic treatment was not inferior to oral prednisone treatment.

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total of approximately 7500 cases in the United States, Europe, and Japan indicate that hearing loss, typically seen among adults, occurs between the ages of 43 and 53 years, with equal sex distribution, and with transient vestibular symptoms present in 28% to 57% of patients.^{1,3-11}

The current standard treatment for idiopathic hearing loss is a tapering course of oral corticosteroid (predni-

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sone or methylprednisolone). This practice is based on a randomized, placebo-controlled trial of oral steroid therapy in 67 patients that showed significantly higher rates of improvement in the steroid-treated group.¹² In this study, hearing recovery was seen in 32% (11 of 34) of participants in the placebo group and in 61% (20 of 33) of the steroid-treated group. The large effect size (0.59) observed with this treatment led to its rapid and widespread adoption. In a subsequent large retrospective study of 266 patients also treated with oral corticosteroids,¹³ improvement was observed in 46% (122 of 266) of the entire study population and in 55% (76 of 139) of patients presenting with a hearing threshold of 60 dB or worse. For this subset with moderate to severe hearing loss, a large effect size was observed (0.64). The steroid-treated group showed a mean 28.0 dB threshold improvement compared with the 22 untreated patients presenting with comparable hearing levels who had a mean improvement of 12.9 dB.

Over the last 15 years, intratympanic corticosteroid treatment by direct injection into the middle ear has gained wide popularity. One theoretical advantage of intratympanic treatment is an increased drug concentration at the target organ. Pharmacokinetic studies in the guinea pig model have shown substantially increased concentration of corticosteroids administered intratympanically compared with systemic administration.^{14,15} However, no adequately powered prospective randomized controlled trial has compared oral and intratympanic steroid treatments to demonstrate that increased local drug concentration leads to improved hearing outcome. In fact, uncontrolled case series have reported intratympanic success rates similar to those reported for oral therapy. One retrospective case series of 26 intratympanically treated patients showed a 27.2-dB mean threshold improvement and 25.4% mean improvement in speech discrimination scores.¹⁶ Another showed intratympanic steroid benefit in 14 of 21 patients (67%).¹⁷

A potential benefit of intratympanic treatment over oral is reduced systemic steroid exposure and associated systemic adverse effects. Adverse effects from oral steroids are well known and usually manageable. They include change in appetite, mood, or sleep pattern; weight gain; gastritis; and increased thirst. More serious medical effects can include hypertension, hyperglycemia, cataract formation, and avascular necrosis of the hip. As noted above, pharmacokinetic studies in animals have shown that local steroid administration to the ear does not produce significant circulating drug levels.^{14,15} Thus anticipated adverse effects of intratympanic treatment would all be local effects, such as ear pain, transient caloric vertigo, tympanic membrane perforation, or infection (otitis media).

With evidence of similar efficacy but other potential advantages of intratympanic over standard oral therapy, we performed a multicenter, randomized, noninferiority trial comparing the efficacy of oral prednisone to intratympanic methylprednisolone for primary treatment of idiopathic hearing loss. A noninferiority design is appropriate when 2 conditions are met: (1) the efficacy of the standard or control treatment and the experimental treatment are expected to be similar, and (2) there may be secondary factors other than efficacy that favor the experimental treatment over the control treatment. In the present study, the known efficacy of oral prednisone and the suggested efficacy of intratympanic steroid seen in several retrospective case series were similar. Because intratympanic treatment reduces systemic steroid exposure and its related adverse effects, one might expect the safety profile of intratympanic treatment to be better than that of oral prednisone. Thus both criteria for a noninferiority design were met.

METHODS

Study Patients

Eligibility criteria included an age of at least 18 years and a unilateral sensorineural hearing loss that developed

within 72 hours and was present for 14 days or less. Pure tone average (PTA), calculated as the arithmetic mean of the hearing thresholds at 500, 1000, 2000, and 4000 Hz in the affected ear, must have been 50 dB or higher, and the affected ear must have been at least 30 dB worse than the contralateral ear in at least 1 of the 4 PTA frequencies. To the best of the participant's knowledge, hearing must have been symmetric prior to onset of sensorineural hearing loss. Because hearing loss is a sporadic condition with no known antecedents, participants were neither known nor expected to have had any preceding otolaryngological encounters. The hearing loss must have been deemed idiopathic following a suitable otolaryngologic evaluation, including medical and otologic history and extensive systems review, head and neck and otologic and neurologic physical examination, audiometry, and imaging to rule-out structural or retrocochlear pathology, such as vestibular schwannoma, stroke, or demyelinating disease. Because oral steroid treatment has long been the standard of care for sudden hearing loss, many patients screened for enrollment in the study had referring physicians that already had initiated this treatment. Exclusion of these patients would have severely hampered subject accrual. Therefore, preenrollment steroid usage of less than 10 days was acceptable as long as audiometric criteria were met on the day of enrollment.

This study was designed to exclude patients with ear disease that could be confused with idiopathic sudden hearing loss and patients with systemic disease who might be at increased risk of adverse effects from steroid treatment. Otologic exclusion criteria included a previous history of hearing loss in either ear, history of fluctuating hearing or Meniere disease, history of chronic inflammatory or suppurative ear disease or cholesteatoma, history of otosclerosis, prior ear surgery of any kind (except ventilating tubes), hearing asymmetry prior to onset, congenital hearing loss, physical trauma or barotrauma to the ear

immediately preceding hearing loss, history of luetic deafness,¹⁸ history of genetic hearing loss with strong family history, or craniofacial or temporal bone malformations revealed by computed tomographic scanning. Systemic exclusion criteria included history of tuberculosis or prophylactic therapy for positive purified protein derivative skin test, insulin-dependent diabetes mellitus, rheumatic disease, active atherosclerotic vascular disease, serious psychiatric disease, prior treatment with chemotherapy agents or other immunosuppressive drugs, pancreatitis, known human immunodeficiency virus, hepatitis C or B infection, chronic renal insufficiency, alcohol abuse, active herpes zoster infection, severe osteoporosis, general anesthesia within 4 weeks of hearing loss onset, history of head and neck cancer, or history of radiation therapy.

Study Design and Procedures

The study protocol, manual of procedures, and informed consent form were approved by the institutional review boards of all participating sites. Recruitment commenced the following month. In addition an independent data and safety monitoring board (DSMB) established by the National Institutes of Health–National Institute on Deafness and Other Communication Disorders also reviewed the protocol prior to patient recruitment. The DSMB routinely monitored the conduct of the ongoing clinical trial for patient safety issues, protocol compliance, and outcome results. The study included 8 visits: a screening visit; a baseline visit to obtain informed consent, enroll, randomize, and initiate treatment; 3 additional safety monitoring visits during the 2-week treatment interval; an immediate posttreatment follow-up visit, and a 2-month (primary), and a 6-month (extended) follow-up visit to assess hearing and safety outcomes.

Interventions

After screening for eligibility, patients consenting to enroll were randomized to receive either oral prednisone or in-

tratympanic methylprednisolone sodium succinate. Permuted block randomization stratified by study site and baseline PTA (<90 dB vs ≥ 90 dB) was accomplished by telephone call to the data coordinating center. The randomization codes were computer generated using SAS software (SAS Institute Inc, Cary, North Carolina). Only personnel at the data coordinating center had access to the codes. The participants and treating physicians were not blinded to treatment. The prednisone group took 60 mg/d for 14 days, followed by a 5-day taper (50 mg, 40 mg, 30 mg, 20 mg, and to 10 mg), for a total of 19 days of treatment. The intratympanic group received four 1-mL doses of 40 mg/mL of methylprednisolone over 2 weeks, with a dose given every 3 to 4 days by injection through the tympanic membrane into the middle ear by an otolaryngologist using an operating microscope. Anesthesia was obtained with topical phenol. Patients were positioned supine with the affected ear slightly up and remained in this position for 30 minutes after the injection. They were instructed to keep water out of the treated ear for the duration of treatment.

Outcomes

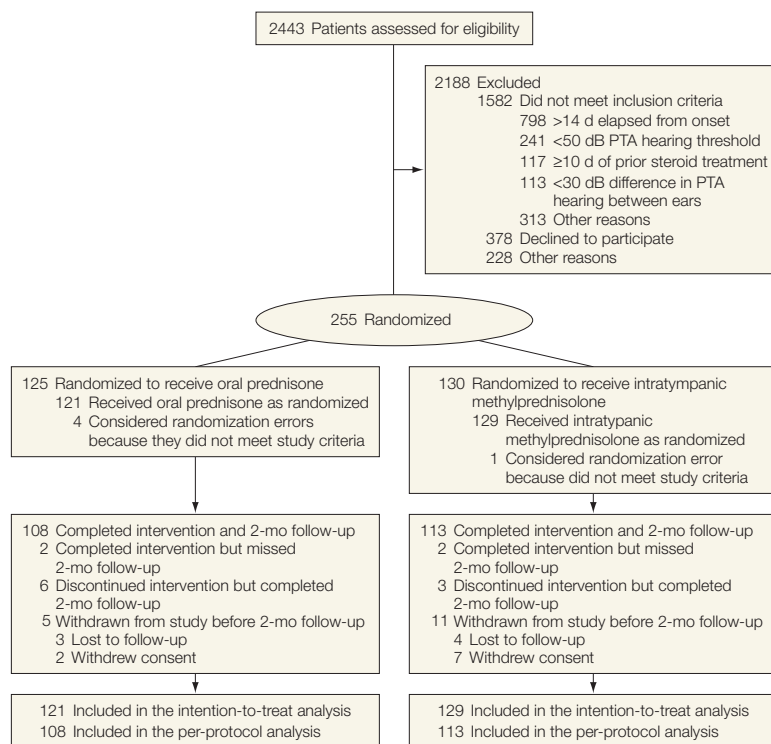
Hearing was tested by air- and bone-conducted pure tone audiometry and speech audiometry at screening, after 1 and 2 weeks of treatment, and at 2 and 6 months of follow-up. Audiologists were blinded to treatment. Pure tone audiometry yields hearing threshold values and speech audiometry yields a word recognition score, the highest percentage (0%-100%; normal $>90\%$) of monosyllabic words identified correctly from digitally recorded standardized 50-word lists presented to each ear of each participant. The primary end point of the study was the change in hearing threshold (dB PTA) from the first audiogram to the 2-month follow-up audiogram. Secondary outcome measures included hearing, PTA at 6 months, difference in PTA between the affected and unaffected ears at 2 and 6 months, word rec-

ognition score at 2 and 6 months, and adverse events. An extensive review of systems questionnaire and visual analog pain scale were completed at every visit. In addition to checking vital signs and otological physical examination at each visit, safety monitoring laboratory studies included complete blood cell count, serum glucose measurement, and urinalysis. Other safety testing was performed at the discretion of the treating physician as indicated by the patient's medical history. Adverse events and serious adverse events were assessed at all study visits.

Statistical Analysis

The primary study hypothesis was that intratympanic methylprednisolone is inferior to oral prednisone for treatment of hearing loss. We define intratympanic to be inferior if the mean post-treatment change in dB PTA of the oral group exceeds that of the intratympanic group by more than 10 dB. Change in PTA has been shown to correlate with patients' reports of communication difficulty and quality of life.¹⁹ Decrease in hearing is steadily related to decreasing life quality.²⁰ The choice of a 10-dB PTA noninferiority criterion for this study was intended to provide a conservative clinical change below which patient outcomes were not clearly differentiable. Our 10 dB criterion is less than half of that reported as the difference between 2 clear groups formed by quality-of-life measures in a large study.²¹ At the same time, a noninferiority boundary must exceed the inherent variability expected by test-retest reliability. This has been shown to be one 5-dB audiometric step, so this value is too small to use for clinical noninferiority.²² The next standard audiometric step (10 dB) is widely considered the smallest change boundary for clinical reporting of asymmetries and air-bone gaps for clinical test procedures.²³

The primary analysis was by intention to treat. The change in PTA was calculated as the difference between the baseline and 2-month follow-up visits. The last available data were used for those who withdrew early (11 intra-

Figure 1. Study Flowchart


PTA indicates pure tone average.

tympanic, 5 oral) or who missed the 2-month visit (2 intratympanic, 2 oral). The change in PTA was set to 0 for study participants who did not complete any follow-up visits (7 intratympanic, 2 oral). We conducted a second analysis in which the change in PTA was set to 0 for all participants who did not complete the 2-month visit while receiving treatment (12 oral, 17 intratympanic). We also conducted a per-protocol analysis, which included those who completed the 2-month visit while receiving treatment (108 oral, 113 intratympanic) because intention-to-treat analyses may bias toward noninferiority. For each of these analyses, the primary hypothesis was evaluated using a 1-sided *t* test.

We also analyzed the primary outcome for the following subgroups: baseline hearing loss (<90-dB PTA, ≥90-dB PTA), men, women, whether dizziness was present at baseline (yes, no), age (<52 years, ≥52 years), days from onset (<7, ≥7), and days of prior steroid

use (<1, ≥1). These subgroups were prespecified in the study protocol. The analysis was the same as that for the primary intention-to-treat analysis. In addition, 2-way analysis of variance with interaction was used to test whether the interaction between treatment group and the variable defining each pair of subgroups was statistically significant.

All other continuous outcomes at 2 months and all continuous outcomes at 6 months were assessed using 2-sided 2-sample *t* tests for a standard null hypothesis of no difference between groups. Categorical data were compared between groups using 2-sided tests, Fisher exact test for binary outcomes, or the χ^2 test for other categorical outcomes. SAS version 9.2 was used for all statistical tests.

The sample size calculation assumed a 10% withdrawal rate, 5% 1-sided α , 90% power, noninferiority margin of 10 dB, and standard deviation of the change in PTA of 25.0. The actual standard deviation was 21.6 and the withdrawal rate

was 11.6% (29 of 250). However, the intention-to-treat analysis included all participants. We used East 3.1 to obtain an interim monitoring rule based on a Lan-DeMets α spending function with O'Brien-Fleming boundaries for rejection of the null hypothesis. The interim monitoring rule comprised 4 equally spaced looks at the data with *P* value boundaries of .0001, .0055, .0219, and .0479. Because of interim analyses, 95.21% confidence intervals (CIs) are presented. The number of randomized participants needed was 127 per group for a total of 254.

RESULTS

Study Patients

Patients from the 16 participating clinical sites were enrolled between December 2004 and October 2009. Originally the recruitment-enrollment period was planned to close in June 2008, but it was extended to meet recruitment targets. The participating sites were both academic and community-based otology referral practices. A total of 2443 patients were screened (FIGURE 1). There were 1582 patients excluded for not meeting eligibility criteria. Of these, 798 (50.4%) were because more than 14 days had elapsed since onset of hearing loss, 241 (11.1%) had a PTA lower than 50 dB, 117 (5.4%) had already had 10 or more days of steroid treatment, and 113 (5.2%) had less than 30-dB PTA difference between ears. The remainder declined to participate or were excluded due to other otologic or medical reasons.

There were 261 patients who consented to participate. Of those who consented, 255 were randomized, of which 250 were included in the intention-to-treat analysis (121 oral, 129 intratympanic) because 5 patients (4 oral, 1 intratympanic) were later found not to meet eligibility criteria. Of the 250 participants included, 16 withdrew from the study (5 oral, 11 intratympanic) up to the 2-month visit. Reasons for study withdrawal included contact lost (3 oral, 4 intratympanic), and withdrew consent (2 oral, 7 intratympanic). Four participants remained in study but

missed the 2-month visit (2 oral, 2 intratympanic), and 9 participants (5 oral, 4 intratympanic) withdrew from treatment but agreed to return for follow-up. Overall, 221 participants (108 [89.3%] oral, 113 [87.6%] intratympanic) who completed the 2-month follow-up visit and continued with the study intervention were included in the per-protocol analysis. After the 2-month visit, another 22 participants withdrew (13 oral, 9 intratympanic). Reasons for study withdrawal after 2 months included contact lost (10 oral, 8 intratympanic) and withdrawal of consent (3 oral, 1 intratympanic).

Between the 2 groups, there were no significant baseline differences in demographics, otologic history, physical characteristics, ear examination, tuning fork test results, neurological examination, cerebellar and vestibular testing, and audiometric measures of pure tone threshold and word recognition scores (TABLE 1). Mean age was 50 years. The male-female ratio was 3:2 in both treatment groups. The mean baseline PTA in the affected and unaf-

ected ears were 86.6 dB (95% CI, 84.0-89.1 dB) and 17.2 dB (95% CI, 15.8-18.7 dB), respectively. Mean word

recognition scores in the affected and unaffected ears were 15.0% (95% CI, 12.3%-17.6%) and 97.9% (95% CI,

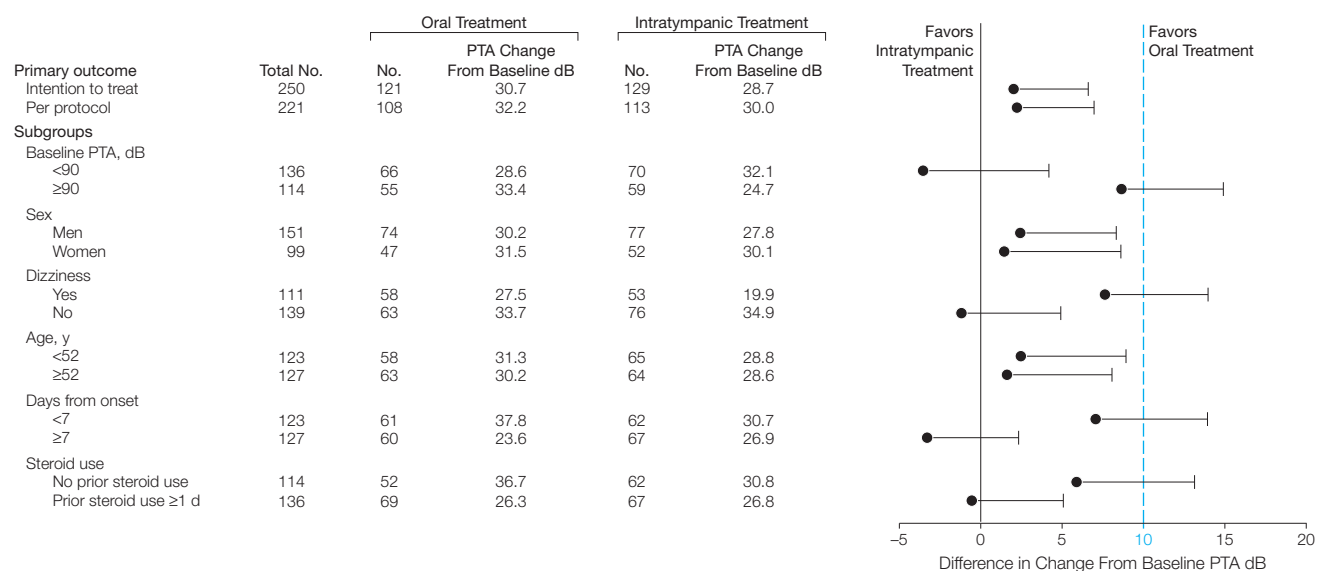
Table 1. Baseline Characteristics^a

| Characteristics | All (N = 250) | Oral Treatment (n = 121) | Intratympanic Treatment (n = 129) |
|--|------------------|--------------------------|-----------------------------------|
| Age, mean (95% CI), y | 50.9 (49.1-52.6) | 50.4 (47.9-52.8) | 51.3 (48.8-53.9) |
| Median (range) | 52.0 (18-85) | 52.0 (18-80) | 51.0 (19-85) |
| Men-women | 1.5:1 | 1.6:1 | 1.5:1 |
| No. of days, mean (95% CI) | | | |
| Study entry from onset of deafness | 6.9 (6.4-7.3) | 6.7 (6.1-7.4) | 7.0 (6.4-7.6) |
| Prior steroid use before study entry | 2.6 (2.2-2.9) | 2.7 (2.2-3.3) | 2.4 (1.9-2.9) |
| Median (25th-75th percentiles) | 1 (0-5) | 1 (0-6) | 1 (0-4) |
| Hearing, mean (95% CI), dB pure tone average | | | |
| Affected ear | 86.6 (84.0-89.1) | 86.7 (82.9-90.6) | 86.4 (82.8-90.0) |
| Unaffected ear | 17.2 (15.8-18.7) | 17.3 (15.4-19.3) | 17.2 (15.1-19.3) |
| Word recognition, mean (95% CI) | | | |
| Affected ear | 15.0 (12.3-17.6) | 14.0 (10.3-17.7) | 15.9 (12.0-19.7) |
| Median (25th-75th percentiles) | 0 (0-27) | 0 (0-22) | 2 (0-28) |
| Unaffected ear | 97.9 (97.3-98.4) | 98.1 (97.4-98.7) | 97.7 (96.8-98.6) |
| Median (25th-75th percentiles) | 100 (98-100) | 100 (98-100) | 100 (98-100) |
| Other symptoms, % | | | |
| Dizziness/vertigo | 111 (44.4) | 58 (47.9) | 53 (41.1) |
| Tinnitus | 209 (83.6) | 103 (85.1) | 106 (82.2) |
| Aural fullness | 173 (69.2) | 85 (70.2) | 88 (68.2) |

Abbreviation: CI, confidence interval.

^aThere was no significant difference in baseline characteristics between the oral and intratympanic treatment groups.

Figure 2. Noninferiority Test of the Change in Pure Tone Average From Baseline to 2 Months



Based on both intent-to-treat (n=250) and per-protocol (n=221) analyses, the point estimate and 95.21% upper confidence interval rejected the hypothesis of inferiority. For the primary analyses only intention-to-treat and per-protocol confidence intervals were adjusted up to 95.21% to account for α spending in interim data looks (See "Methods" section). All subgroup analyses used 95% confidence intervals. Several subgroups (baseline PTA \geq 90 dB, dizziness, days from onset $<$ 7, and no prior steroid use) show a 95% upper confidence interval (error bars) that exceeds the 10 dB noninferiority margin (dashed blue line), indicating inferiority of intratympanic to oral is not rejected. Conversely, point estimates below the 0 dB (no difference boundary) suggest a trend for intratympanic treatment to be better than oral treatment. PTA indicates pure tone average.

97.3%-98.4%), respectively. At presentation, dizziness or vertigo was present in 44% of patients, tinnitus was present in 84%, and aural fullness was present in 69%. Of the 250 patients, 53 (21%) were enrolled within 72 hours of onset, 148 (59%) within 1 week, and 204 (82%) within 10 days. Oral steroid use for 1 to 10 days prior to enrollment in the study was observed in 136 (54.4%) patients.

Hearing Recovery

Primary Outcome. Improvement in PTA at 2 months in the intratympanic methylprednisolone group was not inferior to PTA improvement in the oral prednisone group (FIGURE 2). In the oral prednisone group, PTA improved 30.7 dB compared with 28.7 dB in the intratympanic group. Pure tone average at 2 months averaged 56.0 dB for

the oral group and 57.6 dB for the intratympanic group. The point estimate of the difference between the oral and intratympanic groups in the mean change in PTA from baseline to 2 months after randomization is 2.0 dB. For the final analysis, assigning an α that equals .0479, the 95.21% upper CI is 6.6 dB. Because the upper CI is less than the 10-dB noninferiority margin, we reject inferiority of intratympanic to oral steroid. The *P* value of the difference between the oral and intratympanic groups using a 1-sided *t* test is .002. This comparison included 11 participants (5 oral, 6 intratympanic) who did not complete the 2-month visit and their last available observation was used, and 9 participants (2 oral, 7 intratympanic) who had no follow-up whose change in PTA was set to 0. If the change in PTA is set to 0 for all who did not

complete the 2-month visit while receiving treatment, the mean difference is 2.5 dB (upper CI, 7.2). For the per-protocol analysis, the mean difference is 2.2 dB (upper CI, 7.0). Thus, all 3 analyses support a conclusion of noninferiority.

Subgroups. Among the analyzed subgroups, 2-way analysis of variance tests of interaction indicated significant subgroup differences in treatment effects by baseline level of PTA (*P*=.03) and duration of onset of hearing loss prior to entry into the study (*P*=.05). Intratympanic is not inferior to oral treatment for those with baseline PTA less than 90 dB; for men and women, for those with no dizziness at baseline, for those younger than 52 years or aged 52 years or older, for those with duration of onset 7 days or more, and for those who used steroids

Table 2. Other Hearing Measures^a

| Outcome | Intention-to-Treat Analysis | | | Per-Protocol Analysis | | |
|---|-----------------------------|-------------------------|----------------|-----------------------|-------------------------|----------------|
| | Mean 95% (CI) | | <i>P</i> Value | Mean 95% (CI) | | <i>P</i> Value |
| | Oral Treatment | Intratympanic Treatment | | Oral Treatment | Intratympanic Treatment | |
| Two-mo follow-up | | | | | | |
| No. of patients | 121 | 129 | | 108 | 113 | |
| Word recognition score, % | | | | | | |
| Change from baseline | 34.2 (28.2 to 40.3) | 33.8 (27.8 to 39.7) | .91 | 36.3 (29.9 to 42.7) | 35.5 (29.2 to 41.9) | .87 |
| At 2 mo | 49.1 (42.1 to 56.1) | 50.6 (43.7 to 57.5) | | 51.1 (43.7 to 58.5) | 51.0 (43.7 to 58.3) | |
| Change difference from baseline in pure tone average dB between affected and unaffected ear | 30.2 (26.3 to 34.1) | 28.7 (24.9 to 32.5) | .58 | 31.6 (27.7 to 35.6) | 29.9 (25.9 to 33.8) | .53 |
| Six-mo follow-up | | | | | | |
| No. of patients | 121 | 129 | | 98 | 105 | |
| Pure tone average, dB | | | | | | |
| Change from baseline | 31.7 (27.8 to 35.5) | 29.5 (25.7 to 33.4) | .43 | 32.9 (28.7 to 37.1) | 31.6 (27.5 to 35.7) | .66 |
| Change from 2 mo follow-up | 0.9 (0.1 to 1.7) | 0.8 (0.0 to 1.6) | .81 | 0.7 (0.0 to 1.5) | 1.0 (0.0 to 2.0) | .67 |
| At 6 mo | 55.1 (50.1 to 60.0) | 56.9 (51.2 to 62.5) | | 53.7 (48.2 to 59.2) | 55.1 (49.1 to 61.1) | |
| Word recognition score, % | | | | | | |
| Change from baseline | 35.9 (29.5 to 42.2) | 35.3 (29.3 to 41.4) | .90 | 38.7 (31.7 to 45.7) | 38.6 (32.0 to 45.3) | .99 |
| Change from 2 mo | 1.7 (−0.5 to 3.9) | 1.7 (−0.1 to 3.5) | .99 | 2.4 (−0.2 to 5.1) | 2.0 (−0.2 to 4.3) | .82 |
| At 6 mo | 50.8 (43.8 to 57.9) | 52.3 (45.4 to 59.2) | | 52.9 (45.1 to 60.7) | 54.0 (46.5 to 61.6) | |
| Change difference from baseline in pure tone average dB between affected and unaffected ear | 31.3 (27.5 to 35.2) | 29.8 (26.0 to 33.7) | .59 | 32.5 (28.4 to 36.6) | 32.0 (27.9 to 36.1) | .85 |
| Change difference from 2 mo in pure tone average dB between affected and unaffected ear | 1.1 (0.4 to 1.9) | 1.1 (0.3 to 1.9) | .98 | 1.0 (0.3 to 1.8) | 1.4 (0.5 to 2.4) | .50 |

Abbreviation: CI, confidence interval.

^aOther efficacy measures of hearing outcome at the 2-mo primary end point and 6-mo extended follow-up were considered. Both pure tone average dB and word recognition scores (%) were evaluated.

for 1 or more days prior to study entry. A test of interaction between center and treatment effects was not statistically significant.

Other Hearing Outcomes. Further comparison of hearing recovery in the oral and intratympanic treatment groups also shows that the 2 treatments are comparable at 2 and 6 months (TABLE 2). The frequency of hearing recovery to normal (<30-dB PTA) was 20.7% (25 of 121); to hearing aid range (30- to 90-dB PTA), 66.9% (81 of 121) in the oral treatment group vs 24.8% (32 of 129) and 62.0% (80 of 129) in the intratympanic group, respectively ($P = .69$, χ^2). The frequency of steroid nonresponders (2-month PTA within ± 10 dB of baseline PTA) was 15.7% (19 of 121) for the oral treatment group vs 23.3% (30 of 129) for the intratympanic group ($P = .13$, χ^2). Only 1 participant, in the oral group, showed 2-month hearing worse than baseline, which was between 10 to 20 dB worse. None of the intratympanic participants showed significant worsening of hearing from baseline.

Safety. There were 6 serious adverse events in the intratympanic group and 5 in the oral group during the study. In the intratympanic treatment group, these included osteomyelitis of the toe, leukemia, myocardial infarction, bladder cancer, chest pain due to possible endocarditis, and exacerbation of pre-existing chronic obstructive pulmonary disease. In the oral treatment group, the serious adverse events were myocardial infarction, cerebral hemorrhage, hyponatremia, hospitalization for possible transient ischemic attack, and syncope. The case of hyponatremia arose from worsening of preexistent mild renal insufficiency in a patient with type 2 diabetes that was deemed study-related.

Adverse events are listed in TABLE 3. The P values are for a test comparing the percentage of individual participants reporting at least 1 AE between treatment groups. By the 2-month follow-up visit, there were 663 adverse events reported from the 121 participants receiving oral treatment (5.5/

Table 3. Adverse Events and Serious Adverse Events by Treatment Group

| | Oral Treatment (n = 121) | | Intratympanic Treatment (n = 129) | | <i>P</i> Value ^b |
|------------------------------------|--------------------------------------|---|--------------------------------------|---|-----------------------------|
| | No. of Adverse Events Reported | Unique Patients, No. (%) ^a | No. of Adverse Events Reported | Unique Patients, No. (%) ^a | |
| Adverse event ^c | | | | | |
| Ear pain | 4 | 4 (3.3) | 186 | 70 (54.3) | <.001 |
| Injection pain | | | 98 | 35 (27.1) | |
| Mood change | 55 | 54 (44.6) | 15 | 12 (9.3) | <.001 |
| Dizziness/vertigo | 14 | 13 (10.7) | 49 | 35 (27.1) | .001 |
| Blood glucose problem | 39 | 36 (29.8) | 21 | 21 (16.3) | .02 |
| Sleep change | 44 | 44 (36.4) | 9 | 9 (7.0) | <.001 |
| Appetite change | 28 | 28 (23.1) | 7 | 6 (4.7) | <.001 |
| Dry mouth/thirst | 30 | 30 (24.8) | 5 | 5 (3.9) | <.001 |
| Weight change | 24 | 22 (18.2) | 7 | 7 (5.4) | .003 |
| Ear infection | 2 | 2 (1.7) | 7 | 7 (5.4) | .17 |
| Tympanic membrane perforation | | | 5 | 5 (3.9) | |
| Serious adverse event ^d | | | | | |
| All | 5 | 5 (4.1) | 6 | 6 (4.7) | >.99 |
| Study related | 1 | 1 (0.8) | | | |

^aPercentages are the number of patients who experienced the adverse event at least once/number of randomized patients.

^bThe P values compare the percentage of unique patients experiencing the adverse event at least once between treatment groups.

^cAdverse events accrued by 2-month primary end point showed significant differences between treatment groups. The oral treatment group exhibited predominantly anticipated systemic adverse effects associated with administration of systemic corticosteroids. The intratympanic group primarily exhibited local adverse effects of drug administration by injection into the middle ear. Most adverse events resolved by the 6-month follow-up visit.

^dOf 11 serious adverse events (5 oral, 6 intratympanic), only 1 in the oral treatment group was study related. This list includes all serious adverse events, the most prevalent adverse events and those adverse events with the greatest difference between treatment groups.

participant) and 730 events reported from the 129 participants receiving intratympanic treatment (5.7/participant). Adverse events were reported by 87.6% (106 of 121) of participants in the oral group and 89.9% (116 of 129) in the intratympanic group. The oral treatment group experienced adverse events typical of systemic steroid use that were manageable, including mood, sleep, or appetite changes, increased thirst or dry mouth, elevated blood glucose levels, and abnormal complete blood count. The intratympanic group experienced adverse effects typical of local injection, most often transient pain at the injection site and brief caloric vertigo. Persistent tympanic membrane perforation was seen in 3.9% (5 of 129) of the intratympanic group and none (0 of 121) in the oral group. Otitis media was observed in 4.7% (6 of 129) of the intratympanic treatment group and 0.8% (1 of 121) of the oral group. By

the 6-month follow-up most adverse events had resolved. No patients were withdrawn from treatment for medical treatment of adverse events, but 2 patients in the intratympanic group withdrew consent due to injection site pain.

COMMENT

We have performed a multicenter, randomized comparison of efficacy and safety of oral and intratympanic corticosteroids for primary therapy of idiopathic hearing loss. Overall, we conclude noninferiority of intratympanic steroid to oral prednisone for restoration of hearing loss. Subgroup analyses showed no categories for which the mean PTA difference was 10 dB greater for oral prednisone than for intratympanic steroid treatment, but several subgroups (baseline PTA ≥ 90 dB, dizziness, days from onset < 7 , and no prior steroid use)

failed to reject inferiority because their 95% upper CIs exceeded the 10-dB noninferiority margin. It is of particular clinical importance to note that 2 of these subgroups—baseline PTA of at least 90 dB and dizziness, groups with worse prognosis for hearing recovery—show a trend for better outcome with oral than intratympanic treatment. The magnitude of improvement in word recognition scores at 2 months was not significantly different between treatments. Hearing did not change significantly between the 2-month and 6-month follow-up visits. Both treatments were safe. There were 5 serious adverse events in the oral group and 6 in the intratympanic group, only 1 of which was related to the study drug (oral prednisone). Patients in the oral prednisone group occasionally experienced adverse events typically associated with systemic steroid use.²⁴ These included unpleasant, but not disabling, constitutional symptoms, such as sleep, mood, and appetite changes; increased thirst; and dry mouth, as well as elevated blood glucose and abnormal complete blood count. Patients in the intratympanic methylprednisolone group experienced no significant systemic adverse effects but did experience unpleasant local adverse events, including transient injection site pain, brief caloric vertigo, and occasional cases of otitis media or lingering tympanic membrane perforation. Although safety of the 2 treatments is comparable, intratympanic treatment tends to cause greater discomfort in the form of caloric vertigo, pain, or both. There were 16 withdrawals from the study (5 oral, 11 intratympanic). Of the 11 intratympanic withdrawals, 4 were lost to follow-up, and 2 of the other 7 intratympanic withdrawals were explicitly because of treatment pain. Intratympanic treatment is also less convenient than oral. In routine practice, patients receiving oral treatment need only a single visit to obtain evaluation and a prednisone prescription, whereas patients receiving intratympanic treat-

ment require repeated visits to the physician's office and a period of 30 minutes lying supine after each of the 4 injections.

Delay in diagnosis of hearing loss is a major clinical problem. The common presenting symptoms of aural fullness and muffled hearing are often mistaken for less serious conditions, such as cerumen impaction or congestion. Of 1582 screened patients excluded for not meeting eligibility criteria, 50.4% (798 of 1582) were because more than 14 days had elapsed since onset of hearing loss. Of patients meeting eligibility, 601 (69.8%) of 861 patients declined enrollment, leaving 260 of 861 who participated in the study, an enrollment rate of 30.2%. Both treatments offered in this study are widely available. We found that 143 (23.8%) of 601 participants who declined to enroll were explicitly unwilling to accept random treatment assignment, having specific preferences for which treatment to take, including some who wanted both simultaneously. And another 128 (21.3%) of 601 stated they were uninterested in participating. The choice of audiometric eligibility criteria, medical and otologic exclusion criteria, and the high enrollment of eligible patients contribute to the overall generalizability of our results.

Methylprednisolone was selected for the present study based on preliminary literature on the pharmacokinetics of its distribution in the inner ear.¹⁴ More recent work suggests that dexamethasone also has favorable pharmacokinetics for intratympanic administration.²⁵⁻²⁷ Intratympanic administration of 10 mg/mL of dexamethasone solution causes less pain than 40 mg/mL of methylprednisolone solution. Dexamethasone and methylprednisolone both have potent anti-inflammatory effects, which presumably are relevant in hearing loss treatment. Thus, these 2 drugs might be predicted to have equivalent efficacy at equivalent dosing. Although patient compliance in this study was excellent and only 2 patients receiving intratympanic treatment withdrew due to injection site pain, pain was a common com-

plaint and might be mitigated in practice by use of dexamethasone.

The cost of oral vs intratympanic steroid therapy is very different. Because the primary outcome of this study indicated noninferiority, the relevant economic analysis would be that of cost minimization. A 2-week course of oral prednisone typically costs less than \$10. According to the latest information from the Centers for Medicare & Medicaid Services, intratympanic treatment is reimbursed at a rate of \$172 per injection. The simple cost of 4-dose course of treatment as used here would be \$688. This does not take into account the other possible additional cost of 4 actual visits to the physician's office for treatment, eg, transportation costs, lost wages, or added child care costs.

There are a number of obvious hearing loss treatment questions that remain unanswered by the present study. In future analyses, we hope to explore our data for possible predictors of treatment outcome. Although we observed similar efficacy of oral and intratympanic treatments overall, our subgroup analyses suggested that certain subgroups might achieve greater benefit from one treatment than the other. A number of studies have considered combination therapy using oral plus intratympanic steroid (or other treatments) administered concurrently for primary hearing loss treatment²⁸⁻³¹ or the applicability of intratympanic steroid for salvage treatment in patients who have failed to regain hearing with oral steroid treatment.³²⁻³⁷ None of these studies has been conclusive due to problems of study design, limited sample size, or both.

Overall, intratympanic methylprednisolone was shown to be not inferior to oral prednisone for treatment of idiopathic sudden sensorineural hearing loss. Noninferiority was also indicated for certain subgroups. Both oral and intratympanic treatments are safe but can cause unpleasant adverse effects. The comfort, cost, and convenience of oral prednisone are better than intratympanic treatment. Intratym-

panic treatment is a suitable alternative if there are medical contraindications to oral prednisone.

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