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Audiology In The Sudden Hearing Loss Clinical Trial

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Abstract

Objective—To report the pre- and post treatment population characteristics, and the overall stability of the audiologic outcomes found during the Sudden Hearing Loss Clinical Trial [[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00097448): Identifier NCT00097448].

Study Design—Multi-center, prospective randomized non-inferiority trial of oral v. intratympanic (IT) steroid treatment of sudden sensorineural hearing loss (SSNHL).

Setting—Fifteen academically-based otology practices

Patients—250 patients with unilateral SSNHL presenting within 14 days of onset with 50 dBHL pure tone average hearing threshold in the affected ear.

Intervention—Either 60 mg/day oral prednisone for 14 days with a 5-day taper (121 patients) or four IT doses over 14 days of 40mg/ml methylprednisolone (129 patients).

Main Outcome Measure—Primary endpoint was change in hearing [dB PTA] at 2 months after treatment. Non-inferiority was defined as <10 dB difference in hearing outcome between treatments. In this article, pre- and post treatment hearing findings will be reported in detail.

Results—A general (and stable) effect of treatment, and a specific effect of greater improvement at low frequencies was found in both treatment groups.

Conclusions—Hearing improvements are stable and a significantly greater improvement occurs with lower frequency following either oral or IT steroid treatment of SSNHL.

INTRODUCTION

The Sudden Hearing Loss Clinical Trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00097448): NCT00097448) was a multicenter, prospective, randomized, non-inferiority comparison of oral v. intra-tympanic (IT) treatment with corticosteroid for sudden sensorineural hearing loss (SSNHL). This trial was conducted from December, 2004, through October, 2009, with 4 frequency pure tone average (PTA4; average of 500, 1000, 2000 and 4000 Hz) as the primary outcome variable. All participants were followed for 6 months. The medical results of this trial were published previously.⁽¹⁾ The main result of the clinical trial supported the assertion of the non-inferiority (i.e. no proven difference) of the two arms.

This article will report additional hearing details and results which were not included in the previous publication. These data were collected nationwide with extensive site preparation, independent cross-checking and other methods applied to ensure validity. As a result, these data can form a useful model of clinical expectations in this area. The purpose of this article is limited to the description of the audiology data, and additional justification of the original trial design and interpretation will not be offered. This article will report the overall pre-treatment status of both the affected and unaffected ears in terms pure-tone threshold average PTA and word recognition, stratification of subgroups and outcomes at discrete frequencies.

METHODS

The methods for patient inclusion and treatment used in the clinical trial have been published previously.⁽¹⁾ Briefly, patients were randomized to oral or IT arms if they had a substantial (≥ 50 dB PTA4) rapid loss (< 72 hr.) and passed an extensive battery to rule out Menieres' disease, retrocochlear lesion and any pre-existing history which might contribute to a loss from any other known cause. All participants reported symmetric hearing previous to their SSNHL. The audiology data consisted primarily of a pure tone threshold average (PTA4: average of 500, 1000, 2000, and 4000 Hz thresholds) and word recognition (% correct, 50-item recorded CID W-22 monosyllables; Q/MASS v1).⁽²⁾

All audiologic testing was done by certified Audiologists (CCC-A) using an extensive manual of procedures,⁽³⁾ individual training, and direct supervision by the study's senior audiologist (author CH). Criteria for calibration, materials, test levels and procedures were applied and verified before participants were enrolled. In addition to the local clinic audiogram form, a worksheet form was filled out with all audiometric variables such as masking levels, word presentation levels and materials, and any issues affecting validity. The audiologic evaluation was abstracted onto a data form where coding conventions were applied. These included adding a single 5-dB step to any value found to be out-at-limits. Also, patients with no speech percept in the affected ear, after attempting to respond, were coded as 0% correct.⁽⁴⁾ The data form was reviewed before transmission by the site lead audiologist, who was in contact with the study senior audiologist throughout the study, including monthly conference calls. Data was transmitted to the independent data coordinating center (Hines Cooperative Studies Program Coordinating Center) by the site clinical research coordinators, who were also extensively trained for this study and in constant contact by conference call. Errors were found using computer-applied data value limits and also by checking at each stage of data transmission. When necessary, audiology decisions were referred to the Executive Committee, consisting of the study principal investigator, the senior audiologist and the biostatistician. Statistical analysis was performed using SAS® version 9.3. All statistical tests reported below were two-sided. The criterion for statistical significance was $p = 0.05$.

RESULTS

Figure 1 shows the pure tone averages found for each ear of each patient in the Oral arm, the Intratympanic arm and for both arms combined. Reading from left to right, the first, open box-and-whisker symbols in the three groups show the unaffected ears at the time when each patient was entered into the study. These were found to be predominantly within the normal hearing range. The local clinical P.I. (ENT physician) reported the cause of any hearing loss seen on the unaffected side. Most cases (221/250; 88%) were reported as having no loss on the unaffected side. 18/250 (7%) cases had loss attributed to presbycusis. 10/250 (4%) cases had losses attributed to acoustic trauma or noise exposure, and one case was noted as "other". Patients also reported grossly symmetric hearing (similar to these values) prior to the sudden loss. This indicates that the affected ears resembled these findings just prior to their sudden loss.

The next set of values show the hearing in the affected ear at the time of the sudden loss. All of these losses are greater than or equal to 50 dB PTA since that was the study inclusion criterion (Figure 1, darkest boxes). Approximately half of these cases (114/250; 46% of cases) had losses greater than the study stratification level of 90 dB PTA which was based on the observation of Wilson, et al that such cases responded less well to corticosteroid treatment.⁽⁵⁾ The next box in each of the three groups shows the hearing results at the two-month post treatment point. An equivalent post treatment improvement in PTA4 was found

for both oral and intratympanic groups ($p < 0.0001$). We found improvement (greater than 10 dB PTA4) in the majority (193/250; 77%) of cases from the initial evaluation to that at 2 months post treatment. The average amount of improvement with treatment across the 250 patients was 30 dB (21 s.d.). This effect was shown to be stable at the six month evaluation for both groups.

Figure 2 shows the word recognition scores found in the unaffected ears, and in the affected ears at the pre-treatment, post-treatment (2 months) and longterm (6 months) follow up evaluations. Reading again from left to right, the unaffected ears have scores at or near 100% correct. The affected ears pre-treatment scores show very poor word recognition with many scores at or near 0% correct. There is a clear improvement post treatment ($p < 0.0001$). This effect is also stable as seen at the 6 month post-treatment evaluation.

Figure 3 shows the pre- and post treatment hearing status of study participants using the AAO-HNS Hearing Loss Scale developed for this purpose.(6) Results are divided vertically into decade bins for PTA4, and horizontally into decade bins for word recognition, with the number of participants having such values displayed in each. In general, the concentration of very poor status (lower right corner) is shown to move to better status in many (but not all) cases.

Figure 4 shows the hearing threshold outcome as a function of the initial PTA4 for each of the 250 cases. Each case is plotted showing the pre-treatment PTA4 on the horizontal axis and the amount of improvement (at the 2-month post treatment evaluation) on the vertical axis. This allows appreciation of the likelihood and magnitude of recovery for each treatment type given the presenting severity of the patient's loss. The shaded region marked "no significant improvement" contains all cases where there was 10 dB of improvement or less. What can be seen is that patients (31/250; 12% of cases) across the full range of presenting severity and both treatments did not improve better than 10 dB. There may be some tendency for the less severe cases to approach the maximum recovery limit (which decreases with decreasing initial severity)(7) but this was not statistically proven.

Figure 5 shows a clinical detail regarding the shapes of the presenting audiograms of these patients. Here participants in both treatment arms are combined. Audiogram slope is estimated by subtracting the 500 Hz threshold from that at 4000 Hz. The majority of these cases exhibit flat audiograms and this sample contained few pronounced high- or low-frequency slopes.

Figure 6 shows an important finding which was not reported previously. Here, the amount of threshold improvement by frequency is plotted for both arms combined, with a ± 10 dB "no change" criterion added visually. What can be seen is a trend in which the treatment effect is larger at lower frequencies and progressively decreases with rising frequency. This was also found to be statistically significant ($p < 0.0001$) and conformed to a model of a steadily increasing effect as frequency decreased.

DISCUSSION

The Sudden Hearing Loss Clinical Trial rejected the hypothesis that intratympanic injection was inferior to oral corticosteroid treatment. This finding allows flexibility for clinicians in choosing between these two therapies as the clinical details of each case may indicate. This article shows the audiologic details of this large and rigorously controlled cohort in terms of the presentation, the outcome and the longterm stability of the treatment effects. The general finding of a treatment effect in both arms is supported, as well as observations of individual cases which do not improve. The average amount of improvement with treatment across the 250 patients was 30 dB (21 s.d.). This was very close to the findings of a previous

retrospective study with similar criteria.(8) This treatment effect remained stable at the 6 month evaluation.

A novel finding presented here is that, regardless of the method of corticosteroid administration, the magnitude of improvement was observed to be greater in the lower frequencies. Given the general tendency for flat audiograms seen in Figure 5, the greater effect on lower frequencies does not seem to be an artifact of the starting values. The effect is shown to conform to a statistical model changing smoothly across frequency (SAS GLM). Low frequency sensorineural hearing loss is often considered a hallmark of Meniere's disease, and Meniere's disease has been reported to occur as a late outcome (i.e. years after onset) in 4–8% of cases of sudden sensorineural hearing loss.(9,10) None of our subjects met diagnostic criteria for Meniere's disease, and the short 6-month follow-up of our study does not allow us to draw any conclusions about the ultimate fate of our subjects vis-à-vis development of Meniere's disease. There are also factors other than endolymphatic hydrops that could explain the lability of hearing in lower frequencies. This finding may point the way to further experiments aimed at a better understanding of sudden unilateral sensorineural hearing loss.

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Figure 1.

Box (quartile) and whisker (range) plots are shown describing the pure tone average (PTA4; .5,1.2.4 KHz) for both study arms and for all participants combined. The left-most open boxes show the unaffected ear values. The gray filled boxes show (left to right) the pre-treatment findings on study entry, the 2 month post-treatment findings and the 6-month findings. There was a significant (***) improvement between preand 2-month findings and this was stable at 6 months.

Figure 2.

Similar box-and-whisker plots to those in figure 1 are shown describing the word recognition findings (percent correct; CID W-22 50-item, recorded). These are also arranged with the entry values for unaffected ears on the left and then the pre-, post and longterm scores. Here again, there was a significant (***) improvement between pre- and 2-month findings and this was also stable at 6 months.

Pre- and 2 month post-treatment hearing status for participants in this clinical trial are displayed using the proposed AAO-HNS Hearing Loss Scale developed for this purpose. Decade bins are formed vertically for hearing thresholds (dBPTA4) and horizontally for word recognition scores (percent correct). In the graph on the left no values less than 50 dB PTA4 appear since this was the study inclusion criterion.

Figure 4.

Each individual case can be seen, plotted horizontally by the severity of hearing loss on entry and vertically by the amount of improvement (dB) seen at the 2 month post treatment evaluation. Oral cases are shown using filled circles and intratympanic using open triangles. Losses of 50 dBPTA4 are unlikely to improve beyond 50 dB and this gives rise to the diagonal improvement limit. The bottom shaded area contains those cases where no improvement (>10 dB) was seen.

Figure 5. Pre-treatment audiogram slopes in the affected ears are shown by subtracting the threshold at 500 Hz from that at 4000 Hz. A high frequency slope will result in a positive value along the horizontal axis. Most cases had flat losses.

Figure 6.

Box-and-whisker plots are shown describing the improvement at each of the PTA4 frequencies between pre-treatment and 2 months post treatment with both study arms combined. The central tic shows the median for each set of improvement values and shows a significant trend for better improvement at lower frequencies (SAS GLM, PROC MIXED; $p < 0.0001$).