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United States Multicenter Clinical Trial of the Cochlear Nucleus Hybrid Implant System

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Objectives/Hypothesis: To evaluate the safety and efficacy of acoustic and electric sound processing for individuals with significant residual low-frequency hearing and severe-to-profound high-frequency sensorineural hearing loss.

Study Design: Prospective, single-arm repeated measures, single-subject design.

Methods: Fifty individuals, $\geq$ 18 years old, with low-frequency hearing and severe high-frequency loss were implanted with the Cochlear Nucleus Hybrid L24 implant at 10 investigational sites. Preoperatively, subjects demonstrated consonant-nucleus-consonant word scores of 10% through 60% in the ear to be implanted. Subjects were assessed prospectively, preoperatively, and postoperatively on coprimary endpoints of consonant-nucleus-consonant words, AzBio sentences in noise, and self-assessment measures.

Results: Significant mean improvements were observed for coprimary endpoints: consonant-nucleus-consonant words (35.8 percentage points) and AzBio sentences in noise (32.0 percentage points), both at $P < 0.001$. Ninety-six percent of subjects performed equal or better on speech in quiet and 90% in noise. Eighty-two percent of subjects showed improved performance on speech in quiet and 74% in noise. Self-assessments were positive, corroborating speech perception results.

Conclusion: The Nucleus Hybrid System provides significant improvements in speech intelligibility in quiet and noise for individuals with severe high-frequency loss and some low-frequency hearing. This device expands indications to hearing-impaired individuals who perform poorly with amplification due to bilateral high-frequency hearing loss and who previously were not implant candidates.

Key Words: Cochlear implant, hybrid cochlear implant, hearing preservation, electric-acoustic stimulation, hearing in noise, bimodal stimulation.

Level of Evidence: 2b.

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INTRODUCTION

Hearing loss is a significant public health concern given the deleterious effects that untreated hearing impairment may have on overall physical and cognitive well-being.[1,2] The Hearing Health Foundation reports that nearly 50 million Americans have hearing loss.[3] Sensorineural hearing losses generally have a high-frequency component. This frequency region is essential for good speech understanding in complex listening environments, particularly in noise.[4,5] Individuals with substantial, bilateral high-frequency hearing loss experience hearing difficulties in most aspects of life: at home, on the phone, at work, and in social situations. They can be highly frustrated because existing hearing aid technology cannot overcome the problems of reduced word understanding in quiet and noise.[6–8] Due to their communication problems, they may become isolated, withdrawing from family, colleagues, and friends. With severe hearing loss, areas of minimal or nonfunctioning hair cells or auditory neurons are often present, resulting in cochlear *dead regions* where vibrations of the basilar membrane are not detected via inner hair cells or neurons in that region. Frequencies falling in a dead region are detected via apical or basal spread of vibrations to other cochlear places. Therefore, hearing loss at a given frequency may be greater than indicated by the audiometric threshold.[9] Typically, acoustic amplification of dead regions does not improve speech understanding and may worsen it.[10,11] Individuals with this hearing loss profile may be candidates for electric plus acoustic stimulation in the same ear.

Treatment options for individuals with bilateral, severe ski-slope hearing loss have been limited to state-of-the art amplification, including frequency lowering,[12] in an effort to improve speech intelligibility. These attempts often end with the rejection of hearing aids due to the lack of benefit, leaving the individual with no other alternatives. Studies have shown that an implant with a shorter electrode

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array provides beneficial electric stimulation for high frequencies while preserving acoustic low-frequency hearing, resulting in improved speech understanding.[13,14] Recently, Lenarz et al. described results from a European multicenter study using the Cochlear Ltd., Sydney, Australia, Nucleus Hybrid L24 implant.[15] We report results of the clinical trial leading to U.S. Food and Drug Administration approval of the first-of-its-kind combined electric and acoustic (hybrid) implant system to address the substantial hearing difficulties of individuals not benefitting from amplification and not eligible for a standard cochlear implant (CI).

MATERIALS AND METHODS

This was a prospective, single-arm, multicenter trial to determine the safety and effectiveness of the hybrid system. Subjects were implanted at 10 clinical sites in the United States and served as their own controls in all test conditions. The protocol was approved by the US Food and Drug Administration and relevant institutional review boards, and all participants gave written informed consent.

Fifty individuals aged 18 years or older were enrolled and implanted. The ear selected for implantation had severe ($\geq$ 75 dB HL averaged over 2000, 3000, 4000 Hz) high-frequency sensorineural hearing loss and relatively good low-frequency hearing ($\leq$ 60 dB HL at 125, 250, and 500 Hz). In addition, an aided consonant-nucleus-consonant (CNC) monosyllabic word score of 10% through 60% using an appropriately fit hearing aid was required. Aided word recognition in the contralateral ear was required to be similar or better than the ear to be treated, but not better than 80%. Those with durations of severe or profound hearing loss greater than 30 years and/or onset of hearing loss less than 2 years were excluded.

The protocol included acoustic thresholds measured for each ear preoperatively and postoperatively, at device activation, and 3, 6, and 12 months postactivation. Speech perception was assessed preoperatively using an appropriately fit hearing aid. Postoperatively, the implanted ear was tested at the same postoperative intervals noted above. All signals were presented from a calibrated loudspeaker in front of the subject. Consonant-nucleus-consonant words were presented at 60 dBA; AzBio sentences in noise were presented at 60 dBA in 10-talker babble noise at +5 dB signal-to-noise ratio. To evaluate effectiveness of the hybrid system as used routinely, speech perception outcomes were analyzed in the everyday listening condition, which is listening through the hybrid system in combination with acoustic hearing in the opposite, unimplanted ear.

To gain insight into how hearing impacts quality of life, the validated Speech, Spatial, and Qualities of Hearing Questionnaire (SSQ)[16] was administered as a self-assessment of hearing within three domains: hearing speech in various environments, spatial hearing, and sound qualities. A score of zero corresponded to minimal ability and 10 to complete ability. A device use questionnaire was administered that addressed overall satisfaction with the hybrid system relative to hearing aids.

Surgery for the Hybrid L24 implant (Cochlear) is a modification of that for standard CIs, similar to the description by Gantz et al.[13]; details are provided in the Nucleus Hybrid L24 Implant Surgeon's Guide (Cochlear).[17] After the postauricular incision, the surgeon creates a well bed on the skull posterior to the mastoid and opens the facial recess (posterior tympanotomy) widely to provide good visibility of the round window niche in the middle ear. Although the hybrid implant electrode may be inserted through the round window or cochleostomy, in this trial all electrodes were inserted through a small cochleostomy created just inferior to the round window. After performing the cochleostomy, the surgeon opens the endosteum of the cochlea with a pick just prior to inserting the electrode array. Suctioning of intracochlear fluid is avoided. The array is slowly inserted 16 mm into the scala tympani instead of the 19 to 24 mm that are more typical for standard CIs.

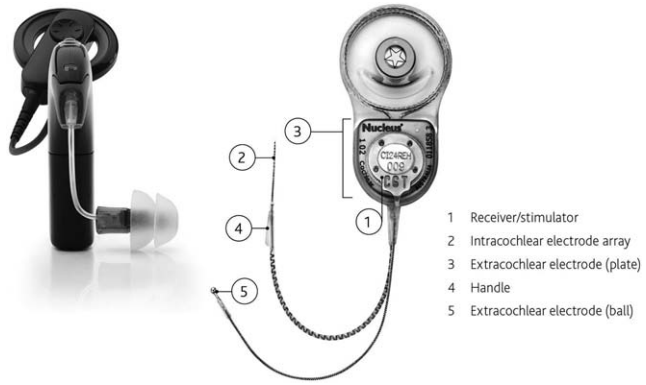

Fig. 1. Image of implanted receiver stimulator and the processor for the Nucleus Hybrid Implant System.

Figure 1 illustrates the Hybrid L24 (Cochlear) implant and processor. The 16-mm straight electrode is very thin and has 22 half-band modiolar-facing electrode contacts to stimulate the basal region of the cochlea, with the intent to maintain apical cochlear structures responsible for low-frequency hearing. The system includes an external processor that integrates electric and acoustic sound processing.

Objectives and Statistical Analyses

Coprimary efficacy hypotheses were that outcomes on CNC words (100 recorded words administered)[18] and AzBio sentences in noise (40 recorded sentences administered)[19] presented through the Hybrid Implant System (Cochlear) would be significantly better at 6 months postimplantation than preoperative performance using a hearing aid. The sample size of 50 subjects exceeded the minimum requirement for 90% statistical power, ensuring adequate power.

Mean differences for subjects on the CNC word and AzBio sentence recognition scores preoperatively and at the 6-month endpoint were analyzed using paired t tests. If there was evidence that assumptions did not hold, a Wilcoxon signed rank test was used. Missing 6-month data were imputed using the last observation carried forward.

Secondary efficacy objectives compared individual preoperative performance with a hearing aid to performance at the 6-month endpoint on CNC words and phonemes and AzBio sentences. Although no formal hypothesis test was conducted for these endpoints, success would be achieved if over 75% of subjects showed equal or better performance from preoperative to postoperative scores using the binomial model.[20]

The primary safety objective was to describe the safety of implantation with the hybrid system. The primary safety endpoint was defined as any surgical and/or device-related event, reported as the number and proportion of individuals experiencing an adverse event.

RESULTS

Demographics

Table I presents demographics for the 50 subjects. Mean age was 64.1 years (standard deviation [SD] = 14.7 years), ranging from 23 to 86.2 years at implantation.

TABLE I.
Demographics and Baseline Clinical Summary.

	Mean ± SD N (min, max)
Age at Implantation in Years	64.1 ± 14.7
	50 (23.0 −86.2)
Duration of Overall Hearing Loss in Years	28.1 ± 14.9
	50 (3.4 −73.9)
Duration of High Frequency Hearing Loss in Years	13.1 ± 7.2
	50 (1.6 −30.1*)
Gender:	N/total (%)
Male	25/50 (50.0%)
Female	25/50 (50.0%)
Preoperative Degree of LF PTA (Implanted Ear):	N/total (%)
Normal (0–25 dB HL)	1/50 (2.0%)
Mild (26 - 40 dB HL)	13/50 (26.0%)
Moderate (41–55 dB HL)	26/50 (52.0%)
Moderate-Severe (56 - 70 dB HL)	10/50 (20.0%)
Preoperative Hearing Aid Use:	N/total (%)
Bilateral Hearing Aids	38/50 (76%)
Unilateral Hearing Aid	9/50 (18%)
No Hearing Aids	3/50 (6%)

HL = hearing loss; LF = low frequency; PTA = pure tone average; SD = standard deviation.

There was a 50/50 split for gender, and 52% of right ears were implanted. Mean duration of overall hearing loss was 28.1 years, and mean duration of severe-to-profound high-frequency loss was 13.1 years. Hearing loss etiologies were: unknown (50%), noise exposure (22%), and familial (20%). Individual cases (8%) were related to ototoxic drugs, autoimmune ear disease, high fever/infection, and noise exposure/viral.

Primary Speech Perception Outcomes

Table II provides a summary of primary outcomes (CNC words and AzBio sentences in noise for the implanted ear). When testing the implanted ear, the contralateral ear was plugged to mitigate its contribution to the speech scores. For CNCs, subjects experienced a significant ($P < 0.001$) improvement of 35.8 (SD = 27.7) percentage points with the hybrid device over a hearing aid preoperatively. Similarly, for AzBio sentences, they experienced a significant ($P < 0.001$) improvement of 32.0 (SD = 29.4) percentage points. One subject missed 6-month assessments, and data were imputed based on the 3-month evaluation. Primary outcome results were consistent under a variety of methods for handling missing data.

Table III presents secondary objective outcomes based on binomial comparisons of preoperative to postoperative changes for CNC words and AzBio sentences for the implanted ear at the 6-month endpoint. The secondary endpoint objectives were met: over 75% of the subjects demonstrated equal or improved performance on CNC words, phonemes, and AzBio sentences with the hybrid implant relative to performance with a hearing aid. Specifically, 96% and 92% of subjects performed equal or better on CNC words and phonemes, respectively, and 90% on AzBio sentences. Furthermore, 82% and 86% showed improved performance on CNC words and phonemes, respectively, and 74% improved on sentences. Results were similar at other study time points (3 and 12 months).

Subgroup Results

The consistency of the primary endpoints for the treated ear was examined across subject subgroups defined by baseline characteristics: gender, age, duration of hearing loss, duration of severe-to-profound high-frequency hearing loss, etiology, and baseline speech perception scores. Results indicated that baseline characteristics gender, age, and duration of hearing loss were the main factors in terms of speech perception outcomes. This was not the case for duration of severe-to-profound high-frequency hearing loss, etiology, and baseline speech scores. Mean benefit scores (i.e., improvement) for females were significantly greater than males for CNC words (females: 48.8%; males: 25.7%) and AzBio tests (females: 42.6%; males: 23.5%) ($P = 0.002$ and 0.02, respectively.) Subjects under the median implantation age of 68 years showed significantly greater benefit for CNCs (< 68 years: 46.6%; > 68 years: 27.8%) ($P = 0.01$) but not AzBio sentences (< 68 years: 41.0%; > 68 years: 25.0%) ($P = 0.05$), although the trend favored younger subjects. The mean benefit for subjects below the median hearing loss duration of 23.5 years was significantly better ($P = 0.01$) than for hearing loss durations above 23.5 years for CNCs (< 23.5 years: 46.2%; > 23.5 years: 27.5%) but not AzBio sentences (< 23.5 years: 40.7%; > 23.5 years: 24.7%) ($P = 0.05$), although the trend favored shorter durations.

TABLE II.
Summary of Co-Primary Efficacy Endpoints.

(N=50)†	Acoustic Alone Preoperative Mean ± S.D.	Hybrid Mode 6 Months Postactivation Mean ± S.D.	Percentage Point Change Mean ± S.D. (95% C.I)
Word scores*	28.4% ± 14.7%	64.2% ± 26.6%	35.8 ± 27.7 (27.9, 43.7)
AzBio scores*	16.3% ± 14.4%	48.3% ± 31.3%	32.0 ± 29.4 (23.7, 40.4)

*Word scores: $p < 0.001$; AzBio scores: $p < 0.001$
†One subject missed 6-month assessments and data were imputed based on the 3-month evaluation.
S.D. = standard deviation.

TABLE III.
Summary of Secondary Objectives for CNC Words and AzBio Sentences in Noise.

	CNC Words	CNC Phonemes	AzBio in Noise
Proportion of subjects with postoperative score equal to or better than preoperative score:	96%	92%	90%
Proportion of subjects with postoperative score better than preoperative score:	82%	86%	74%

CNC = consonant-nucleus-consonant.

Bilateral Outcomes

Mean differences for CNC words and AzBio sentences in noise at 6-months postactivation, using the implant and contralateral hearing aid, were preoperatively compared to bilateral amplification. For CNCs, subjects (N = 49) showed significant ($P < 0.001$) improvement of 34.7 percentage points (SD = 17.4) compared to bilateral amplification. For AzBio sentences, subjects (N = 49) showed significant ($P < 0.001$) improvement of 33.0 percentage points (SD = 23.5) compared to bilateral amplification. No subject showed a significant decrement preoperatively to postoperatively on either measure. At the 6-month endpoint, all subjects performed equal or better than preoperatively with bilateral amplification with hearing aids.

Patient Self-Assessments

Forty-eight subjects completed the SSQ preoperatively using hearing aids and after 6 months using the hybrid system in the everyday listening condition. For the Speech Hearing Scale, subjects improved significantly ($P < 0.001$), showing a mean change score of 2.2 (SD = 1.8). On the Spatial Hearing Scale, there was a significant ($P < 0.003$) mean change score of .9 (SD = 2.0); on the Sound Quality Scale, subjects experienced significantly ($P < 0.001$) improved mean change of 1.3 (SD = 2.0).

Of the 48 subjects who completed the device use survey, four (8%) were "satisfied"/"very satisfied" with preoperative hearing aids, whereas 38 (79%) were "satisfied"/"very satisfied" with the hybrid device.

Adverse Events

Sixty-five adverse events involving 34 of 50 subjects were reported (Table IV). The type and frequency of events were consistent with those reported in cochlear implantation (e.g., electrode open or short circuits, postoperative dizziness, changes in tinnitus) or other mastoid operations; no unanticipated adverse events were reported. Fifty events were medical/surgical in nature and included instances of increased tinnitus, vertigo, and other symptoms associated with a mastoidectomy with facial recess approach used in cochlear implantation. It should be noted that the nine adverse events reporting of dizziness, imbalance, and vertigo were likely reported by a few patients and not nine separate patients; one could have symptoms of dizziness,

TABLE IV.
Number and Percentage of Adverse Events Observed for Hybrid L24 Subjects.

Event	Number of Events	Percentage of Events	Number of Subjects with Event	Percentage of Subjects
Profound/total loss	22	33.8%	22	44.0%
Open/short-circuited electrodes	11	16.9%	11	22.0%
Increased tinnitus	6	9.2%	6	12.0%
Tinnitus not present preoperatively	6	9.2%	6	12.0%
Dizziness	3	4.6%	3	6.0%
Dizziness with change in hearing	2	3.1%	2	4.0%
Increased tinnitus with change in hearing	2	3.1%	2	4.0%
Skin irritation due to externals	2	3.1%	2	4.0%
Sound quality issue	2	3.1%	2	4.0%
Decrease in performance	1	1.5%	1	2.0%
Imbalance	1	1.5%	1	2.0%
Imbalance with change in hearing	1	1.5%	1	2.0%
Increased impedances with change in hearing	1	1.5%	1	2.0%
Local stitch infection	1	1.5%	1	2.0%
Overstimulation	1	1.5%	1	2.0%
Pain in implant ear	1	1.5%	1	2.0%
Vertiginous symptoms with change in hearing	1	1.5%	1	2.0%
Vertigo	1	1.5%	1	2.0%
Total	65			

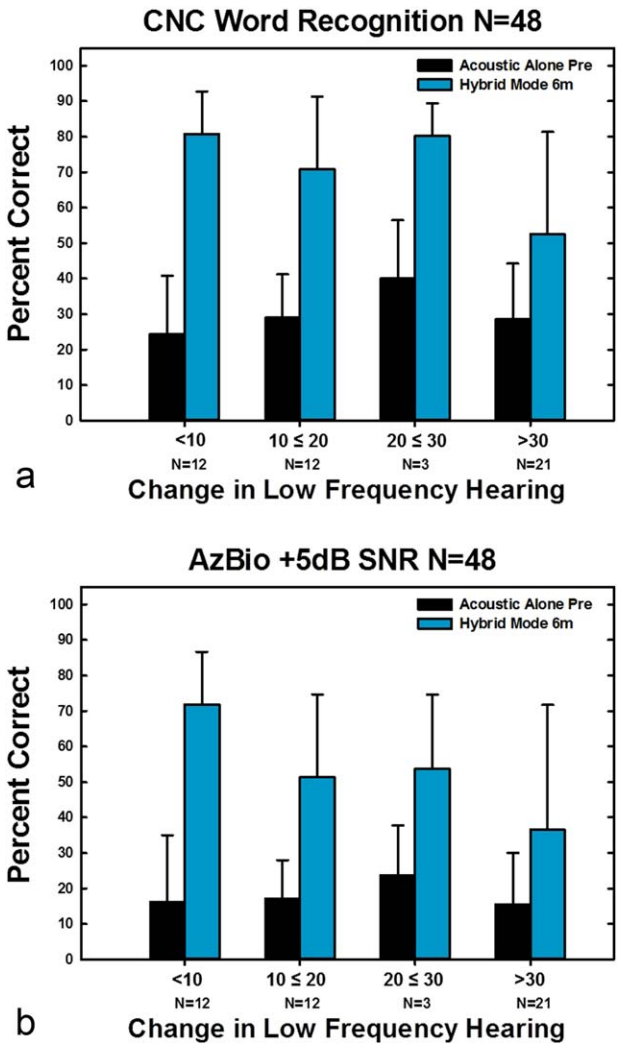

Fig. 2. (a) CNC word scores for subjects with < 10, 10–20, 20–30, and > 30 dB of hearing loss at 6 months post-cochelar implant activation. The number of subjects in each category of hearing loss is shown. (b) AzBio +5 dB signal-to-noise ratio scores for subjects with < 10, 10–20, 20–30, and > 30 dB of hearing loss at 6 months post-cochlear implant activation. The number of subjects in each category of hearing loss is shown.
Abbreviations: CNC = consonant-nucleus-consonant; SNR = signal-to-noise ratio. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

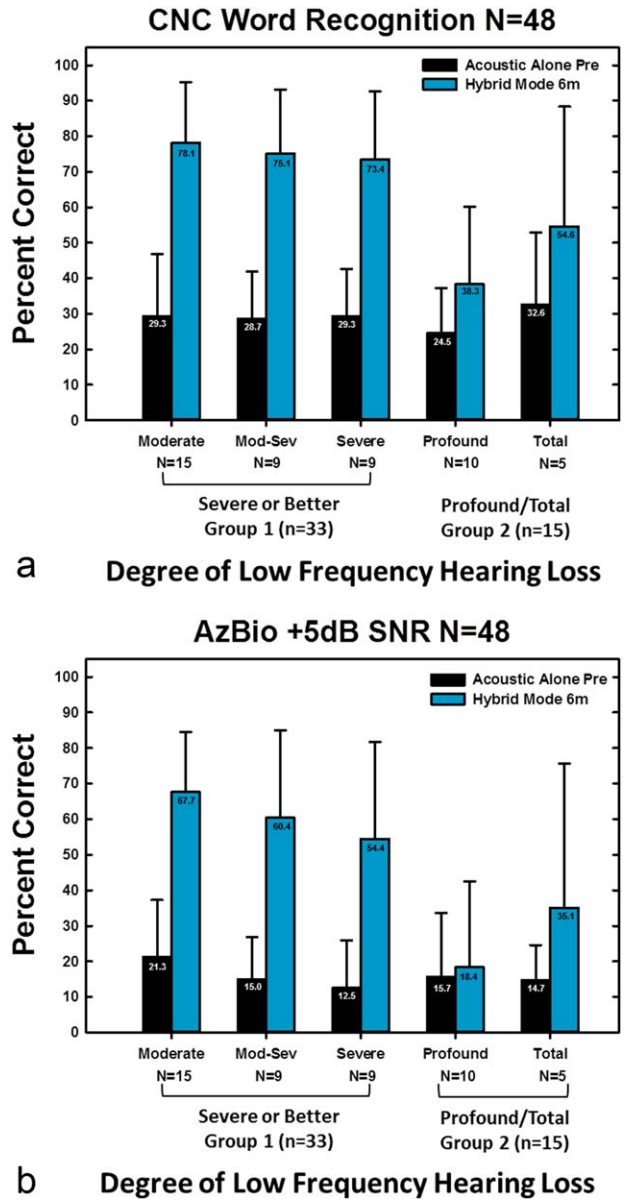

Fig. 3. (a) The CNC word scores for subjects in each category of low-frequency hearing loss. The number of subjects in each category of low-frequency hearing loss is shown. (b) The AzBio +5 dB signal to noise ratio scores for subjects in each category of low-frequency hearing loss. The number of subjects in each category of low-frequency hearing loss is shown.
Abbreviations: CNC=consonant-nucleus-consonant; SNR = signal-to-noise ratio. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

imbalance, and vertigo. This trial specified implanting subjects with functional low-frequency acoustic hearing. Unlike prior CI trials, this was the first to quantify changes in residual hearing; any changes in preoperative to postoperative hearing sensitivity were measured throughout the study period. Changes resulting in profound (> 90 dB HL) hearing loss were reported as anticipated adverse events. At 6-months postactivation, 66% of subjects (33 of 50) retained functional acoustic sensitivity determined by a 5-frequency pure tone average (125, 250, 500, 750, 1000 Hz) of a severe degree or better (≤ 90 dB HL). The degree of hearing loss and the number of subjects in each hearing loss category and their postintervention outcomes are depicted in Figure 2a and b. In addition, the amount of residual hearing and the number of subjects in each category and their postintervention outcomes are depicted in Figure 3a and 3b. Subjects with aidable, residual hearing performed better that those without aidable, residual hearing. However, even if subjects had no residual, aidable hearing, they performed better in the CI electric-only condition than preoperatively with hearing aids. Regarding 17 subjects who did not maintain functional acoustic hearing, five chose to have the hybrid implant explanted and replaced with a standard CI. These revision surgeries were successful, with full insertions achieved in all cases.

Improved speech perception of varying degrees was observed compared to that obtained preoperatively with a hearing aid and at the most recent hybrid evaluation prior to revision surgery. Based on self-assessments, these subjects were satisfied with their outcomes.

There were 15 device-related events. Apart from cases of profound hearing loss, all but two events (one sound quality issue and one decreased performance) were resolved as of database closure.

Association of baseline characteristics with adverse events, including profound hearing loss, was examined by univariate Cox proportional hazards regression models. Baseline characteristics evaluated included age at implantation, hearing loss duration, severe-to-profound hearing loss duration, etiology, and preoperative speech perception. None were found to be significantly associated with either outcome of an adverse event or profound hearing loss.

DISCUSSION

Results from this study support the conclusion that the Nucleus Hybrid System (Cochlear) delivers significantly improved speech understanding in quiet and noise compared to a hearing aid for individuals with bilateral, severe high-frequency hearing loss. Ninety percent of subjects achieved the same or better performance on both speech perception measures when listening with the hybrid system. When using both ears, all subjects performed equal or better than preoperatively on both measures. The SSQ self-assessment supported speech intelligibility results, with significant improvement on all scales and with greatest improvement on the Hearing Speech Scale. On overall listening satisfaction, the number of individuals satisfied increased from 8% preoperatively with amplification to 79% with the hybrid system.

This system delivers important high-frequency information through electrical stimulation and the opportunity to combine it with beneficial low-frequency residual hearing in one or both ears. Outcomes for five subjects undergoing revision surgery suggest that a standard CI remains a viable treatment when hybrid implantation does not meet expectations.

Current hearing aid technology often cannot provide audible, clear high-frequency sound for individuals with this type of hearing loss. Individuals with substantial high-frequency losses frequently have nonfunctional inner and outer hair cells; therefore, amplification cannot be effective. Individuals with precipitously sloping losses predictably are frustrated due to significant communication struggles; they regularly reject amplification, leaving them with no alternative treatments prior to availability of the hybrid system.

Limitations to the study include the nonrandomized design, limited sample size, and duration of follow-up. Using subjects as their own control enables clinically meaningful comparisons that account for patient heterogeneity, and use of standardized objective measures of hearing helps ensure validity. The effect and sample size were large enough to produce statistically significant improvements after 6 months follow-up; additional longer term follow-up for safety and study of the device in larger and diverse subgroups is important.

CONCLUSION

The hybrid system successfully provides high-frequency sensitivity essential for good speech understanding. Typically, this is not accessible through amplification for individuals with bilateral severe high-frequency hearing loss and beneficial, aidable low-frequency hearing. This system is a new and effective treatment that provides clinically significant improvements in speech understanding through integrated electric and acoustic stimulation in the implanted ear, with additional benefit when listening using both ears—thus fulfilling a need in individuals who to date have had no other treatment options.

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