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RESEARCH ARTICLE

Objective and subjective evaluations of the Nurotron Venus cochlear implant system via animal experiments and clinical trials

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ABSTRACT

Conclusion: This study described objective and subjective evaluations of the Nurotron® Venus™ Cochlear Implant System and indicated that this system produced a satisfactory performance.

Objective: To observe the performance of the Nurotron® Venus™ cochlear implant (CI) system via electrophysiological and psychophysical evaluations.

Methods: A 26-electrode CI system was specially designed. The performance of MRI in animal and cadaveric head experiments, EABR in cats experiment, the correlation between ESRT and C level, and psychophysics evaluations in clinical trials were observed.

Results: In the animal and cadaveric head experiments, magnet dislocation could not be prevented in the 1.5 T MRI without removal of the internal magnet. The EABR was clearly elicited in cat experiment. In the clinical trial, the ESRT was strongly correlated with C level (p < 0.001). The human clinical trial involving 57 post-lingually deafened native Mandarin-speaking patients was performed. Residual hearing protection in the implanted ear at each audiometric frequency was observed in 27.5–46.3% patients post-operatively. A pitch ranking test revealed that place pitches were generally ordered from apical to basal electrodes. The recognitions of the perceptions of 301 disyllabic words, environment sounds, disyllabic words, and numerals were significantly better than the pre-operative performance and reached plateaus.

KEYWORDS

Cochlear implant, electrically evoked auditory brainstem responses (EABR), electrically evoked stapedius reflex threshold (ESRT), MRI, Nurotron, pitch ranking, speech perception

INTRODUCTION

A number of cochlear implant systems have been developed for people with profound hearing loss. Generally, it is believed that a greater number of intra-cochlear electrodes improve the user’s resolution and provide greater sound detail [1,2]. Electrode array placement has been recognized as a potentially important factor in the efficacy of the responses of the residual nerve-fibers within the cochlea to electrical stimulation [3]. To restore hearing to people with severe-to-profound deafness, a 26-electrode auditory prosthesis—Nurotron® Venus™ cochlear implant system was specially designed. This system included a flexible electrode array to reduce the damage to the cochlea and preserve the residual hearing to the greatest extent possible.

In August 2011, the Food and Drug Administration of China approved the commercial release of the Nurotron® Venus™ Cochlear Implant System. A group of 57 post-lingually deafened, native Mandarin-speaking patients using the Nurotron® Venus™ Cochlear Implant System completed their 36-month experiences. The purpose of this study was to present the results of electrophysiological and psychophysical evaluations of these cochlear implant recipients [4].

MATERIALS AND METHODS

Study design

A 26-electrode auditory prosthesis, i.e. the Nurotron® Venus™ cochlear implant system, was specially designed and approved for commercial release by the Food and Drug Administration in China. The authors present assessments of this system’s performance based on 1.5-Tesla (T) MRI experiments with animals and cadaveric heads, electrically evoked auditory brainstem responses (EABRs) observed in cats, the correlation...
between the electrically evoked stapedius reflex threshold (ESRT) and the maximum comfort level (C level), and psychophysical evaluations in a clinical trial.

MRI compatibility in cat and cadaveric head experiments

The Nurotron® device’s magnetic resonance imaging (MRI) compatibility was tested and found to meet the international EN45502 safety standards for static magnetic fields up to 1.5 T. The major concerns of imaging with the magnet in situ are the forces generated by the magnet and the MRI equipment and the risk of magnet displacement and associated discomfort.

To evaluate the effects of the 1.5 T MRI on the Nurotron® Venus™ Cochlear Implant System, the prosthesis, including the internal magnet, was implanted into a cat and maintained for a period of 6 weeks. During the MRI experiment, the animal was anesthetized, and all of the external components were removed. A crepe bandage was firmly wrapped around the animal’s head prior to the MRI scan (Figure 1). The cat was then transported to a SIEMENS SONATA 1.5 T MRI scanner and placed on the table of the scanner in a position in which the implanted ear was facing up.

To evaluate the effect of the 1.5 T MRI on the internal magnet, a fresh-frozen cadaveric head was unilaterally implanted with a Nurotron® Venus™ Cochlear Implant that included the internal magnet. All external components were removed, and a crepe bandage was firmly wrapped around the head prior to the MRI scan. The fresh-frozen cadaveric head was then transported.
to the SIEMENS SONATA 1.5 T MRI scanner and placed onto the table of the scanner with the implanted ear facing up.

To examine the displacement caused by the MRI scan, X-ray scans were performed before and after the MRI experiment. The phenomenon that the internal magnet was totally moved out of the shell was defined as complete displacement. If the internal magnet was moved out partly, the angle between the magnet and the plane of the coil was recorded.

**Electrophysiological evaluation in cat experiments and clinical trials**

**Cat experiments**

Prior to the human clinical trial, Nurotron\textsuperscript{\textregistered} Venus\textsuperscript{TM} Cochlear Implant Systems were implanted into two normal-hearing cats. The EABRs of the cats were recorded. A 200-μs/phase biphasic current pulse was applied, and the potential difference between the scalp electrodes was averaged over 1000 repetitions.

**Clinical trials**

To evaluate the performances of the cochlear implants [5] and the functions of the auditory systems of cochlear implant users and to assess the relationship between the ESRTs and C levels, post-lingually deafened patients were recruited.

The inclusion criteria were as follows: (1) 6–65 years of age; (2) bilateral post-linguistic severe-to-profound sensorineural hearing loss (≥ 85 dB HL average hearing threshold of 0.5, 1, 2, and 4 kHz); (3) ≤ 30% average open-set sentence recognition in the ear to be implanted and ≤ 50% average closed-set recognition (http://www.tigerspeech.com) [6]; and (4) the patients satisfied the standard cochlear implantation candidacy criteria issued by the Chinese Ministry of Health [7].

The exclusion criteria were the following: (1) inner ear malformations and/or auditory nerve absences; (2) otitis media; (3) serious mental diseases; (4) patients who did not understand or refused the clinical evaluation; and (5) patients who did not satisfy the standard cochlear implantation candidacy criteria issued by the Chinese Ministry of Health [7].

Twenty-three volunteer patients (outpatients of the Eye Ear Nose & Throat Hospital of Shanghai Fudan University) with post-lingual deafness were recruited and were implanted with Nurotron\textsuperscript{\textregistered} Venus\textsuperscript{TM} Cochlear Implant Systems. Sixteen of these patients (female/male ratio = 7/9, 20 ± 9 years old, range = 7–35 years) agreed to participate in and ultimately completed this part of the research. All 16 patients with the Nurotron\textsuperscript{\textregistered} Venus\textsuperscript{TM} Cochlear Implant System were evaluated 1 month after cochlear implantation surgery with full insertion of the electrode array. The causes of deafness included head trauma, familial progressive disease, and deafness of unknown cause. All subjects were stimulated using the m-n strategy. Prior to the measurement of the ESRT, the C levels were tested. The ESRTs were assessed with the acoustic impedance electro- audiometer (Madsen Electronics ZODIAC 091) and the programming station of the Nurotron\textsuperscript{\textregistered} system. The C levels were obtained via standard procedures. The audiologist had access to the ESRTs during programming. Nine cochlear electrodes (electrodes 1, 2, 3, 11, 12, 13, 21, 22, and 23) were stimulated as the tested electrodes.

**Psychophysical evaluation in clinical trials**

Regarding its application in humans, the Food and Drug Administration in China approved human clinical trials of the Nurotron\textsuperscript{\textregistered} Venus\textsuperscript{TM} Cochlear Implant System in October 2009, and the commercial release of this system in August 2011.

Post-lingually deafened patients were recruited. The inclusion criteria and exclusion criteria are described above. Sixty post-lingually deafened patients (female/male ratio = 34/26, 26 ± 12 years old, range = 6–59 years; implantation age = 25.94 ± 12.38 years old) participated in the Nurotron\textsuperscript{\textregistered} cochlear implant clinical trial from December 2009 to October 2010. The investigation was conducted at the following five cochlear implant clinics in China: Shanghai Fudan University (n = 23); Beijing People’s Liberation Army General Hospital (PLA General Hospital, n = 15); Beijing Tongren Hospital (n = 10); Zhejiang University (n = 7); and Chongqing Medical University (n = 5). At the end of the first year, 57 of the 60 participants completed their 12-month evaluations, and the remaining three participants were lost to follow-up. Forty-eight of the 60 participants completed their 36-month evaluations. At the 36-month follow-up, no acute adverse events caused by the medical devices were observed. Twelve participants were lost to follow-up for reasons that included distance, time problems, and phone number and address changes.

The speech recognition tests included the House sentence recognition test, the 301 (PLA General Hospital) sentence recognition test, the environment sounds, vowels, consonants, numerals, disyllabic words, and multi-word recognition (http://www.tigerspeech.com) [6].
Residual hearing of pure tone audiometry

To establish a baseline auditory function, the patients were pre-operatively evaluated under unaided conditions [8]. The unaided hearing thresholds of each ear were measured with headphones. The thresholds were measured at 250, 500, 1000, 2000, and 4000 Hz. The responses that were perceived as auditory were recorded. The data from the patients who exhibited hesitancy in the testing process were not included. To categorize the PTA threshold changes at each frequency, the changes in the threshold values for each participant were subdivided. We adopted the schema proposed by James et al. [9] and adapted by Garcia-Ibanez et al. [10] as follows: ≤10 dB (clinically insignificant/gold standard); 11–20 dB (clinically significant with moderate preservation); 21–40 dB (clinically significant with marginal preservation); and >40 dB or no measurable response (no preservation).

Pitch ranking

Six subjects (S1, S2, S3, S4, S5, and S6) among the 57 Nurotron® CI users (6 month experience with CI) performed the speech recognition and electrode pitch ranking tests. The electrode pitch ranking test was performed to evaluate the place–pitch perception abilities of CI users.

The testing methods of the electrode pitch ranking tests were similar to those employed in the studies of Townshend et al. [11] and Nelson et al. [12]. The stimulus was composed of 50-μs/phase biphasic current pulses, 890 pps, 500 ms pulse train, and presented in monopolar mode (MP1 + 2). The subjects reported that all electrodes were in tonotopic order based on the subjective pitch of the stimuli that was swept across the array. The parameters were chosen according to each subject’s clinical map. Once the subject’s active electrodes had been selected, the initial current level of each electrode was set at 75% of the patients’ clinical maximum comfort level. In the pitch ranking step, all of the adjacent electrode pairs were selected. For S1, S2, and S4, a total of 23 pairs of stimuli ({$E_1, E_2$},{$E_2, E_3$},…{$E_{23}, E_{24}$}) were chosen. The sensitivity index or $d’$ was calculated from the percentage of correct scores obtained from the subject’s response. The sensitivity index $d’$ can be considered to be a measure of the perceptual difference between the two intervals. In this study, $d’$ provided a measure of the discriminability between pairs of electrodes. If the place–pitch represented a single perceptual dimension, the $d’$ sensitivity should be accumulated; e.g. the sum of $d’$ for the ranking of electrodes E1–E2 and E2–E3 should equal $d’$ for the ranking of electrodes E1–E3. A graphical user interface was developed to control the presentation of the test stimuli and collect the responses from the subjects [13].

Speech/word perception

The close-set tests (environment sounds, numerals, and disyllabic words) were evaluated. Each test had eight alternatives, and the subject had to choose one of them (http://www.tigerspeech.com). The open-set test (PLA General Hospital disyllabic words) was also performed.

Institutional Review Board approval

The experimental protocols were reviewed and approved by the Animal Care and Use Committee and the Institutional Review Board. Each patient signed an informed consent form prior to participation.

Statistical analysis

Data were analyzed using SPSS Statistics 16, and $p < 0.05$ was adopted as indicative of statistical significance.

Results

MRI compatibility in cat and cadaveric head experiments

An X-ray was taken prior to the MRI scan. Fifteen minutes after the axial and coronal plane MRI scan, an X-ray was acquired and compared to the X-ray that was acquired prior to the MRI scan. Displacement of the internal magnet occurred in the live cat (complete displacement) and the cadaveric head (the angle between the magnet and the plane of the coil was 67.6°) (Figure 2A–D).

Following the removal of the internal magnet, one fresh-frozen cadaveric head was implanted unilaterally with a Nurotron® Venus™ Cochlear Implant System. The fresh-frozen cadaveric head with a crepe bandage wrapped firmly around it was subjected to an MRI in the same scan condition. After the scan, no displacement of the internal device occurred following internal magnet removal (Figure 2E).

Electrophysiological evaluation in cat experiments and clinical trials

Cat experiments

The Nurotron® Venus™ Cochlear Implant System was implanted into two normal-hearing cats. The EABRs of
the cats were recorded. Figure 3 illustrates typical EABR waveforms that were recorded in one of the cats. The positive peaks (II, III) were clearly observed, and the latencies were 1.78- and 2.45-ms, respectively [14]. The threshold EABR of this animal was 150 CL.

Clinical trials
Sixteen post-lingually deafened CI users with Nurotron® Venus™ Cochlear Implant Systems were evaluated at 1 month after cochlear implantation surgery. The ESRT and C levels were tested in all subjects, and the results
were observed by the audiologist. ESRTs were detected in 91 out of the 144 tested electrodes (63.2%). Figure 4 shows the correlation between the ESRT and the C level, and the $R^2$ linear $= 0.835$ ($R = 0.91, p < 0.001$), indicating that the ESRT is highly correlated with C level obtained through subjective judgments.

**Psychophysical evaluation in clinical trials**

**Residual hearing of pure tone audiometry**

Fifty-four (94.7%) of 57 patients exhibited measurable hearing pre-operatively at two or more audiometric frequencies in the implanted ear. Post-operatively, the unaided acoustic hearing thresholds were re-measured in the implanted ear at the 1-month post-surgery evaluation. The threshold changes at each frequency are shown in Table I.

**Pitch ranking**

Six subjects (S1, S2, S3, S4, S5, and S6) of the 57 Nurotron® CI users (6 month experience with CI) performed speech recognition, and electrode pitch ranking tests. Table II illustrates the information for the six subjects. Figure 5 demonstrates the findings of the electrode tone sequencing tests for these six subjects. The horizontal co-ordinate represents cochlear electrodes #1–24 (from the cochlear apical electrode to the basal electrode), and the vertical co-ordinate represents their corresponding tone sensitivities ($d'$). All of the subjects acquired the tone perception from ‘low’ to ‘high’ as expected.

The results indicated that the place pitch was generally ordered from the apical to basal electrodes. The apical
electrodes were judged to be lower in pitch than the basal electrodes. Large individual differences were found. A comparison of the pitch and speech performances revealed that the speech recognition results were related to the place–pitch perception abilities of the CI users; however, this relationship was limited by ceiling effects.

**Speech/word perception**

The close-set tests (environment sounds, numerals, and disyllabic words) were evaluated. Each test involved eight alternatives, and the subject was required to choose one of these alternatives (http://www.tigerspeech.com). The open-set test (PLA General Hospital disyllabic words) was also performed. Figure 6 illustrates the percentages of correct recognition as functions of time for the environment sounds, disyllabic words, and numerals. Overall, the results of the environment sound recognition were similar to those of the sentence recognition. Although variations across subjects were substantial (1-month), recognition improved significantly as a function of time \[ F(7,426) = 199, \ p < 0.01 \] to reach a plateau after only 2-months of use. The disyllabic words and numerals recognitions varied widely among the

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Etiology</th>
<th>Numbers of active electrode</th>
<th>Speech perception (close)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>Male</td>
<td>23</td>
<td>Sudden deafness</td>
<td>24</td>
<td>92.9%</td>
</tr>
<tr>
<td>S2</td>
<td>Female</td>
<td>35</td>
<td>Ototoxic deafness</td>
<td>24</td>
<td>100%</td>
</tr>
<tr>
<td>S3</td>
<td>Male</td>
<td>26</td>
<td>Ototoxic deafness</td>
<td>23</td>
<td>100%</td>
</tr>
<tr>
<td>S4</td>
<td>Male</td>
<td>20</td>
<td>Ototoxic deafness</td>
<td>22</td>
<td>97.1%</td>
</tr>
<tr>
<td>S5</td>
<td>Male</td>
<td>36</td>
<td>Noise-induced deafness</td>
<td>24</td>
<td>100%</td>
</tr>
<tr>
<td>S6</td>
<td>Female</td>
<td>20</td>
<td>Ototoxic deafness</td>
<td>19</td>
<td>92.9%</td>
</tr>
</tbody>
</table>
subjects (1- and 2-month) and significantly improved as a function of time \([F(7, 426) = 206, p < 0.01; F(7, 426) = 194, p < 0.01]\) to reach a plateau after only 4-months of use. This result is similar to those of previous studies of consonant and vowel recognition.

Figure 6 also illustrates that the open-set test results on the PLA General Hospital disyllabic words recognition task varied widely among the subjects (1, 2, 4, 6), but improved significantly as a function of implant usage over the 36-month period \([F(7, 426) = 166, p < 0.01]\). Post-hoc analysis revealed significant improvements from an average score of 5% correct prior to cochlear implantation to 18%, 33%, 54%, and 67% correct at the 1-, 2-, 4-, and 6-month testing times, respectively \((p < 0.05)\). The cochlear implant performance reached a plateau after 12 months, with a peak recognition rate of 85% at the 36-month evaluation.

**Discussion**

The Nurotron® Venus™ array has 26 pure-platinum contacts, which is more than any other electrode array in the world (the Nucleus has 22 electrodes, the MED-EL has 12, and the Advanced bionics has 16) and is capable of spanning the speech frequency range within the cochlea.

Devices from three major manufacturers, including the Nucleus CI24, MED-EL Pulsar CI100, and Advanced Bionics HiRes 90k [15], were examined by Tam et al. [15], who performed a series of *in vitro* tests that revealed that no alterations in device function following the acquisition of images of sufficient quality via MRI scanning in a 1.5-T machine. The present study in the cat and cadaveric head found that MRI examinations involving the Nurotron® Venus™ cochlear implant should only be performed when there is a strong medical indication, and surgical removal of the internal magnet should be performed before scanning in 1.5-T MRI machines.

The positive peaks of the EABRs in the cat experience were similar to those reported in a study by Kretzmer et al. [16] in which Clarion II high-focus implants from the Advanced Bionics Corporation CI that were manufactured with smaller 6-electrode arrays for use
in cats were examined. The waveforms of the EABR revealed that the Nurotron® Venus™ Cochlear Implant System was able to effectively stimulate the feline auditory system.

In clinical trials, ESRTs were detected in 91 of the 144 tested electrodes (63.2%), and this result is similar to that reported in Battmer’s research (70%) [17]. ESRT programs and behavioral testing programs are strongly correlated, and the use of the ESRT has been suggested to be a useful means for creating a cochlear implant speech processor program [18]. The threshold of the ESRT might be an important parameter for helping doctors and audiologists estimate the C level during the tuning of cochlear devices. Similar to the results of Hodges with the Nucleus cochlear implants [19], in the present study of the Nurotron® Venus™ Cochlear Implant System, the correlation between the ESRT and C level indicated that the ESRT was highly correlated with C level, as assessed through subjective judgments.

Post-operatively, the unaided acoustic hearing thresholds were re-measured only in the implanted ears only at the 1-month post-surgery evaluation to assess the residual hearing following surgery [20,21]. In a study of Nucleus 24 Contour array [22], clinically insignificant (change in 250 Hz PTA ≤10 dB) was observed in 7% patients, and clinically significant with moderate preservation (change in 250 Hz between 11–20 dB) was observed in 19% patients. In this study, clinically insignificant (change in 250 Hz, PTA ≤10 dB) was observed in 31.7% patients, and clinically significant with moderate preservation (change in 250 Hz between 11–20 dB) was observed in 7.31% patients. This success rate can be ascribed to the atraumatic insertion of the Nurotron® Venus™ electrode array and indicates that the Nurotron® Venus™ cochlear implant system exhibited a satisfactory performance in terms of residual hearing protection.

The pitch ranking test was used to systematically investigate the place–pitch perceptions based on the electrical hearing and revealed that the place pitch was generally tonotopic from the apical to the basal electrodes. Large individual differences were observed, and these differences indicate that the current signal processing functions of the CI system can provide sufficient information to understand speech. Kong and Zeng [23] and Xu et al. [24] observed that much finer spectral information (8–12 channels) is needed for tone recognition in spoken Mandarin and Cantonese. Previous clinical trial research has demonstrated that the sound signal characteristics transmitted by the sound coding strategy of the Nurotron® cochlear implant can provide excellent speech recognition effects.

When a CI user recognizes complicated signals such as music, his/her tone perception ability at the electrical stimulation hearing site determines the auditory effect to a certain extent. Previous studies [4,25] of this 26-electrode cochlear implant system revealed that all of the subjects exhibited significant improvements in quiet and reached the level of ceiling effects in close-set tests (Mandarin consonants, vowels, and tones) and open-set tests (House sentence recognition and PLA General Hospital sentence recognition) of Mandarin. Our findings are consistent with those of previous research. In the present study, the results of close-set tests that included the recognition of environment sounds, disyllabic words, and numerals exhibited improvements and plateaued after 2–4 months of usage. In the open-set test of the present study, the PLA General Hospital disyllabic words recognition significantly improved, and the greater recognition was 85%, which was observed at the 36-month evaluation. Both the close-set and open-set evaluations indicated that the Nurotron® Venus™ cochlear implant system exhibited a satisfactory performance in this study.

Using a large sample size and a long observation time (3 years), this study demonstrated significant improvements in the perceptual recognition. A clear trend of progress with the time of the implant usage was also observed.

**Conclusion**

This study describes objective and subjective evaluations of the Nurotron® Venus™ Cochlear Implant System based on animal experiments and clinical trials. The Nurotron® Venus™ array has 26 pure-platinum contacts. The studies of MRI compatibility in cat and cadaveric head experiments, EABR in cats experiment, ESRT and C level, and residual hearing of pure tone audiometry in clinical trials revealed the steady performance of this system. The results of the pitch ranking test in clinical trials suggested that this system can provide sufficient information for the understanding of speech. The large sample size and long observation time of this clinical study demonstrated that the Mandarin speech recognition significantly improved from the pre-implantation level to reach a plateau of high-level performance following a maximum of 12 months of usage. The results of this study indicate that the Nurotron® Venus™ cochlear implant system exhibits a satisfactory performance for patients.

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