CHAPTER 7

Long-term evaluation of treatment of chronic, therapeutically refractory tinnitus with neurostimulation of the vestibulocochlear nerve

H. Bartels
M.J. Staal
A.F. Holm
J.J.A. Mooij
F.W.J. Albers

Abstract

Objective
Long-term evaluation of treatment of chronic, therapeutically refractory tinnitus by means of chronic electrical stimulation of the vestibulocochlear nerve.

Patients
Inclusion criteria were severe, chronic, therapeutically refractory, unilateral tinnitus and severe hearing loss at the ipsilateral site. Out of six patients, four patients were selected for long-term evaluation. Two patients were not evaluated because of preliminary dropout.

Material and methods
A stimulation electrode was placed around the vestibulocochlear nerve through a retrosigmoid approach and connected to a subcutaneously-positioned pulse generator via an extension cable. Follow-up was performed three months and 42.5 months after implantation. Three measures for treatment outcome were used. First, effect sizes were determined by means of the total THI-score using Cohen’s formula. Second, general and tinnitus-specific audiometric tests were performed in on- and off-conditions of the neurostimulation system. Third, recordings were noted for tinnitus severity and treatment success on a visual analogue scale.

Results
All four patients reported successful treatment with neurostimulation. The effect size after three months was 0.7, indicating an average effect, while the effect size measured during long-term follow-up was 1.75, indicating a substantial effect with major clinical implications. No changes in hearing level for both ears were measured. The neurostimulation system did not change the tinnitus pitch in any of the patients, and resulted in a minimal reduction of tinnitus loudness in only two patients. In all four patients the original tinnitus sound was replaced by another, pleasantly-perceived sound. The average VAS-score of perceived tinnitus severity was reduced from 8 to 3.25. The average VAS-score for treatment success was 7.25.

Conclusions
The long-term follow-up of neurostimulation treatment for chronic tinnitus shows promising results. Long-term results were better than those determined after a three-month follow-up. In all patients the tinnitus was replaced by another, pleasantly-perceived sound. Further studies are needed before accepting neurostimulation as a treatment modality for chronic, therapeutically refractory tinnitus.
Introduction

Tinnitus is a phantom perception of meaningless sounds in absence of an external acoustic stimulus (1;2), which is chronic and may affect everyday activities and the quality of life experienced. This subjective tinnitus is only experienced by the patient and cannot be objectified by an external observer (3). About 2–5% of the general population is severely affected by tinnitus (4;5), experiencing anxiety, depression, and great negative implications on concentration, sleep and relaxation.

Tinnitus has been described in association with nearly every form of ear pathology but is most frequently related to cochlear dysfunction (1). Deprivation of input, abnormal input or injury to peripheral receptors are causes of tinnitus at the peripheral level. They result in a decreased afferent input to the central auditory pathways, inducing alterations in several structures of the CNS in order to compensate for and adapt to these altering demands or reduced input.

Mechanisms such as neural plasticity, reorganization of receptive, tonotopical fields and loss of inhibition might induce hyperactivity and the spread of activity in several structures of the auditory pathways. Enlargement of excitatory receptive fields and redirection of neuronal information induce activity in parts of the brain that are normally not involved in auditory perception. Tinnitus may be the perceptual consequence of this hyperactivity in the brain, which can be described as a maladaptive manifestation of neural plasticity within the auditory system. Because of the dynamically modifiable character of the CNS, the effects of neural plasticity on the CNS are potentially reversible (6) if the distorted patterns of input are restored. This creates opportunities for the development of treatment modalities.

Electrical stimulation of the auditory system as a treatment modality for tinnitus has been investigated in humans over the last decades, varying from transcutaneous stimulation at the outer ear to direct intracranial stimulation of the central auditory pathway structures. Primarily, transcutaneous and transtympanic electrical stimulation were investigated and several studies showed some tinnitus relief (7-10). Using non-invasive, transcranial magnetic stimulation, several investigators proved able to reduce the perceived tinnitus strength at least during the time of stimulation (11-13). Direct electrical stimulation of the cochlea has been performed by means of a round window electrode (14), promontory stimulation (15) and cochlear implants (16-18). Suppressing tinnitus by means of the electrical stimulation of higher structures of the auditory pathways has been investigated at the brainstem (19) and the auditory cortex in humans (11;20). The tonotopically organized auditory system and the thalamocortical loop interactions (21) explain the effects of these neurostimulation modalities on tinnitus perception.

Many similarities have been described between the pathophysiological processes of tinnitus and other hyperexcitability manifestations such as neuropathic pain, muscle spasm, phantom pain, phonophobia and hyperpathia (6). Based on the analogy of treatment modalities used in other hyperexcitability disorders, it might be possible to develop new treatment modalities for tinnitus. For several years neurostimulation devices have been used to treat various chronic pain syndromes.
showed to be intractable to other treatment modalities. Neurostimulation has been performed in neural structures in and outside the central nervous system, and encompasses various techniques such as Transcutaneous Electrical Nerve Stimulation (TENS), Peripheral Nerve Stimulation, Spinal Cord Stimulation, Deep Brain Stimulation and cortical stimulation (22-25). Spinal Cord Stimulation is described as being effective in the treatment of neuropathic pain syndromes such as reflex sympathetic dystrophy, peripheral nerve injury, post-amputation pain, spinal cord lesions, and ischemic pain syndromes as seen in angina pectoris and peripheral vascular disease (26,27). The Spinal Cord Stimulation device consists of an electrode lead connected to a pulse generator via an extension lead. The electrode is implanted epidurally at a vertebral level that is determined by the location of the pain. Electrical pulses transmitted to the electrodes excite fibers in the spinal cord, thereby generating paresthesia in the pain region and decreasing the pain sensation.

Following current ideas about neurostimulation of hyperexcitability disorders such as tinnitus and chronic pain, in 2001 we developed a new treatment modality using neurostimulation of the auditory pathways. By means of chronic electrical vestibulocochlear nerve stimulation, we initially treated six patients with therapeutically refractory tinnitus, primarily studying the feasibility and safety aspects (28). The long-term clinical evaluation of this treatment modality in four of the six patients will be described in this paper.

Patients and method

Patients

The most important inclusion criteria for the initial pilot study of treatment with neurostimulation were patients with unilateral, severe, chronic, therapeutically refractory tinnitus and severe hearing loss at the site of the tinnitus. Patients with bilateral tinnitus, hearing thresholds less than 80 dB HL at all frequencies (ranging from 125 Hz up to 8 kHz) and with any other treatment available were excluded from the initial study.

Six patients were treated with neurostimulation during the initial study; four patients were selected for long-term evaluation. Two patients did not participate because of preliminary dropout.

In one of these two dropouts the neurostimulation system proved to be unsuccessful after a period of three months post intervention. As the pulse generator was surgically removed during this period, long-term evaluation could not be performed in this case. The second dropout reported treatment success during the three-month evaluation period (Patient 2 (28)). Other medical health and psychiatric problems, not related to the tinnitus, led to an unreliable measurement of treatment outcome. This patient was therefore excluded from long-term evaluation.

Patient characteristics are given in Table 1: they concern one man and three women, between 54 and 64 years of age. The initial pathology that caused the tinnitus and severe hearing loss was an idiopathic sudden deafness in three patients and deafness as a result of cochlear surgery in the fourth patient. The average
duration of the tinnitus sensation before implantation was 4.5 years (range 1–8 years). The average time between surgery and long-term evaluation was 42.5 months (range 30–49 months).

**Operation technique**

The implanted device consisted of a custom made quadripolar stimulation lead (Model 2958-25; Medtronic Corporation, Minneapolis), a pulse generator (Itrel 3, Model 7425; Medtronic) and an extension cable (Model 7496-51; Medtronic) (Figure 1). The stimulation electrode was placed around the vestibulocochlear nerve through a retrosigmoid approach (Figure 2). The slit circular electrode housing of the lead with four contact plates was placed around the vestibulocochlear nerve after arachnoideal dissection of the eighth from the seventh nerve, as close to the brain stem as possible. The electrode was connected to the subclavicular, subcutaneously-placed pulse generator via an extension cable.

The pulse generator was programmed (Model 7432 programmer; Medtronic) with an individually modifiable range of stimulation parameters. The waveforms of the stimulus pulses are unmodulated monophasic and charge balanced (to prevent a net charge admission to the stimulated tissues). The stimulation parameters were set using a doctor’s computerized programmer, which communicates transcutaneously with the implanted generator. A patient programmer (Model 7434; Medtronic) enables an on-and-off switch and a slight variation of the voltage within the preset window.

Two of the six implants were funded by Medtronic.
Figure 1. The Neurostimulation system

Figure 2. Implantation of the stimulation lead around the vestibulocochlear nerve
Evaluation measurements
Follow-up was performed three months and on average 42.5 months after implantation. Tinnitus severity was measured by means of the Tinnitus Handicap Inventory (THI), designed and validated by Newman in 1996 (29). The THI questionnaire consists of twenty-five questions and a three-point Likert scale. Ratings of the total THI-score vary from 0 to 100 points; a total THI-rating of at least 58 points indicates that tinnitus is causing a severe handicap.

Effect sizes of neurostimulation treatment were determined according to Cohen’s formula (30), noted in Appendix 1. By means of the pooled standard deviations and averages of total THI-scores before intervention and during follow-up, the effect size of neurostimulation treatment could be calculated. An effect size is an easily used, statistical measure for determining the success of treatment reported. The effect-size value gives an indication of clinical relevance, as described in Appendix 1.

General and tinnitus-specific audiometric tests and click-evoked otoacoustic emission tests in the contralateral ear were performed in on- and off-conditions of the neurostimulation system.

The patients were asked to score their tinnitus severity on a visual analogue scale (0 = no tinnitus, 10 = extremely severe tinnitus) before intervention and during long-term evaluation, and to give their opinion about success of treatment (0 = not successful, 10 = very successful).

The neurostimulation treatment in the six patients was approved by the ethics committee of the University Medical Hospital Groningen, the Netherlands, in 2001.

Results
Two electrodes were positioned on the right side, two on the left side. The stimulation parameters were installed according to the patients’ reported effect on their tinnitus perception. These individual stimulation parameters are provided in Table 2. No side effects from neurostimulation treatment were reported during long-term evaluation.

The total THI-scores during long-term follow-up showed remarkable reductions in three of the four patients. The reduction of the total THI-score during long-term follow-up in the fourth patient was minimal because of a generally perceived reduction in the quality of life caused by other medical health problems not associated with tinnitus. The average total THI-score during long-term follow-up (average score 38) was remarkably reduced when compared to the total THI-score from the three-month follow-up (average score 55). The total THI-score for two of the patients was not reduced during the three-month follow-up since neurostimulation achieved its reduction of tinnitus severity in these patients at only around six months post intervention. The average total THI-scores, standard deviations and associated effect sizes during these three periods are noted in Table 1.
Using Cohen’s formula, we calculated the effect size of neurostimulation treatment by means of the total THI-scores before intervention and during the two periods of follow-up. The effect size of neurostimulation treatment during the three-month follow-up was 0.7, indicating an average effect; the calculated effect size during long-term follow-up was 1.75, indicating a substantial effect with great clinical implications.

Standard and tinnitus-specific audiometric tests and click-evoked otoacoustic emission tests were performed during on and off-conditions of the neurostimulation system. General audiometric testing did not show any major difference between on and off-situations, either in the ipsilateral or in the contralateral ear. Tinnitus matching frequency remained similar during on and off-conditions and tinnitus matching intensity only minimally decreased in two of the four patients (Table 1). Both frequency and intensity were determined in the contralateral ear.

In none of the patients did the tinnitus disappear during the on-condition of the neurostimulation system. Before intervention all patients reported that their tinnitus consisted of a combination of several noises of aching loudness, worsening during periods of stress and emotion. The neurostimulation system transformed this intrusive combination of noises into a single, pleasantly-perceived noise.

Table 1. Patient characteristics during long-term evaluation and effect size

<table>
<thead>
<tr>
<th>Patient</th>
<th>age (years)</th>
<th>duration (years)</th>
<th>intervention date</th>
<th>tinnitus matching frequency</th>
<th>tinnitus matching intensity</th>
<th>total THI-score, before intervention and during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>on = off (dB)</td>
<td>on = off (dB)</td>
<td>before 3 months 42.5 months</td>
</tr>
<tr>
<td>A. male</td>
<td>55</td>
<td>2</td>
<td>May'01</td>
<td>2 kHz 55</td>
<td>40</td>
<td>62 58 56</td>
</tr>
<tr>
<td>B. female</td>
<td>55</td>
<td>1</td>
<td>July '01</td>
<td>3 kHz 70</td>
<td>70</td>
<td>100 100 60</td>
</tr>
<tr>
<td>C. female</td>
<td>64</td>
<td>7</td>
<td>Jan '03</td>
<td>2 kHz 85</td>
<td>80</td>
<td>58 58 26</td>
</tr>
<tr>
<td>D. female</td>
<td>54</td>
<td>8</td>
<td>Oct '01</td>
<td>4 kHz 70</td>
<td>70</td>
<td>88 4 10</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td>77</td>
<td>55</td>
<td>38</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td>20.3</td>
<td>39.3</td>
<td>24.1</td>
</tr>
<tr>
<td>effect size</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>0.70</td>
<td>1.75</td>
</tr>
</tbody>
</table>
Table 2. Individual stimulation parameters

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mode of stimulation</th>
<th>Amplitude (volt)</th>
<th>Frequency (Herz)</th>
<th>Pulse width (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Monopolar</td>
<td>0.7</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>B</td>
<td>Monopolar</td>
<td>0.95</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>C</td>
<td>Bipolar</td>
<td>0.15</td>
<td>60</td>
<td>150</td>
</tr>
<tr>
<td>D</td>
<td>Monopolar</td>
<td>2.0</td>
<td>60</td>
<td>150</td>
</tr>
</tbody>
</table>

Three visual analogue scales were used, which described tinnitus severity before implantation, currently perceived tinnitus severity and reported treatment success. The recordings on the visual analogue scale are described in Table 3. The average score for tinnitus severity before intervention was 8.00, and 3.25 during long-term follow-up. The average score for reported success of neurostimulation treatment rated by the four patients was 7.25. If these four patients had to decide whether to undergo this treatment a second time, all of them would agree to participate.

Table 3. Recordings on visual analogue scale

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tinnitus severity before intervention</th>
<th>Tinnitus severity long-term follow-up</th>
<th>Reported success of neurostimulation treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8</td>
<td>6</td>
<td>6*</td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>C</td>
<td>9</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>D</td>
<td>8</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>average</td>
<td>8.00</td>
<td>3.25</td>
<td>7.25</td>
</tr>
</tbody>
</table>

* success of neurostimulation treatment is negatively influenced by other medical problems not associated with tinnitus, primarily concerning vertigo and severe hearing loss.

Discussion

In this study, performed after an initial pilot study, the long-term results were evaluated for a new treatment modality for chronic tinnitus, consisting of chronic electrical neurostimulation of the vestibulocochlear nerve. The results of this study showed a successful reduction in perceived tinnitus severity in four out of the six patients initially treated.
In none of the four evaluated patients did the tinnitus disappear (as determined during the off-condition of the neurostimulation system); instead it was transformed into another, pleasantly-perceived sound (as determined during the on-condition of the neurostimulation system). The effects of neurostimulation of the auditory pathways persisted as long as the neurostimulation system was turned on. An increased reduction of total THI-scores during long-term follow-up as compared to the total THI-scores during three-month follow-up was measured; two patients responded quickly to the electrical neurostimulation of the vestibulocochlear nerve, the other two patients reported a tinnitus reduction at about six months post intervention. The reported reduction of tinnitus severity could not be objectified using tinnitus-specific audiometric tests.

Several theories have been proposed during the last decade in order to explain the generation and perception of tinnitus. Alteration of hair cell physiology has long been assumed to be the triggering mechanism for tinnitus induction (1;31). Microvascular compression of the auditory nerve has been described as resulting in focal deafferentiation, leading to tinnitus generation in the central auditory system (32). Many studies support the hypothesis that tinnitus is generated in the central parts of the auditory system and that neural plasticity plays an important role in the generation of tinnitus (6;31;33). The general role of neural plasticity of the CNS is its adaptation to altered input and to the effects induced by injury or disease. Early manifestations of neural plasticity observed immediately after a lesion of peripheral structures have been attributed to a loss of GABAergic surround inhibition and the unmasking of dormant, preexisting neural circuits (6;34;35). Surround inhibition is concerned with a general inhibition of excitatory tonotopical receptive fields by GABA, and may be reduced as a result of distorted input (21;36;37). The consequence of reduced surround inhibition is the development of hyperexcitation regions in the CNS, assumed to have perceptual consequences such as tinnitus.

The effects of neural plasticity that only occur weeks or months later are characterized by processes such as axonal sprouting, synaptic changes and reorganization in tonotopic receptive fields (6;34;38);(39). These processes may lead to increased hyperactivity in the auditory pathways and a spread of activity to brain regions that are normally not involved in hearing. The auditory pathways actually have adapted too much to an altered input, resulting in the generation of tinnitus.

The effects induced by chronic, electrical neurostimulation of the vestibulocochlear nerve can be divided into easily obtainable effects, as seen in the quickly responding patients, and into more structural effects, as seen in those patients reported to be successfully treated after a period of six months. We hypothesize that the early effects of neurostimulation might be attributed to restoration of the early manifestations of neural plasticity, concerning a restored (surround) inhibition and a restored masking of dormant, preexisting neural circuits. In the two late-responding subjects, we hypothesize that neurostimulation was needed to restore the late effects of neural plasticity to a more structural basis, as characterized by processes such as axonal sprouting and synaptic changes (6;34;38).
The tonotopic organization of the cochlea is represented in several structures of the auditory pathway: the auditory nerve, the dorsal cochlear nucleus (DCN), the inferior colliculus (IC) and the auditory cortex (40;41). The functional organization of these tonotopical receptive fields is not statically fixed, but seems to alter and adapt dynamically in response to changing patterns of input, intrinsic dynamics of the different neuronal loop interactions (39), and manifestations of neural plasticity (42;43). Reduced surround inhibition, axonal sprouting and reorganization within tonotopical receptive fields result in hyperactivity and lateral spread of neural activity (21;36;37). Cortical and subcortical regions that have lost their normal input, take over the frequency of adjacent neuronal areas (44;45). Consequently, an excess of tonotopical neurons will represent a very restricted frequency area of the cochlea. Spontaneous and stimulated activity of these neurons will in turn activate more neurons at the same time. Increased synchrony of spontaneous and activated neural activity in the regions of these perilesion frequencies is expected to have perceptual consequences such as tinnitus (41;46).

The fact that the tinnitus pitch could not be altered by electrical neurostimulation of the vestibulocochlear nerve might indicate that the late manifestations of neural plasticity induce effects in the auditory system with a structural basis. Neurostimulation of the auditory pathways seems unable to restore these structural manifestations and lesions in the tonotopic organization. Whether neurostimulation applied exactly to the distorted frequency area within the tonotopic organization will then be able to alter the tinnitus pitch is a question that will need further investigation. This might be achieved through suitable stimulation of the frequency area related to the tinnitus pitch on the auditory nerve. Nevertheless, this would only be possible in high frequency tinnitus, since these high frequencies are located in the outer border of the auditory nerve (32;47;48).

Tinnitus loudness only minimally decreased in two of the patients, possibly indicating that the neurostimulation system slightly reduced the hyperactivity and synchrony of neural activity. This reduction in synchronically-neural activity might result in a decrease in tinnitus loudness. Why this reduction in tinnitus loudness did not occur in all patients needs to be investigated.

Electrical neurostimulation of the vestibulocochlear nerve at this location in the auditory system is a novel approach in the treatment of chronic tinnitus. Other currently investigated, previously described neurostimulation approaches in the treatment of tinnitus differ from our approach in the location of stimulation of the auditory system. Electrical stimulation of the auditory system by means of transcutaneous or transtympanic electrodes, round window or promontory electrodes and cochlear implants, perform direct, electrical stimulation on the cochlea. The advantages of these methods of stimulation as compared to our method lie in their less invasive stimulation technique, and so the related risks might be less. Disadvantages of these stimulation methods may be cochlear damage in a still functional ear, reduced effectiveness of the treatment in a severely damaged or anatomically abnormal cochlea and the general risks associated with otologic surgery.
Our method of electrical neurostimulation is located rostral to the spiral ganglion and therefore stimulates the distal part of the vestibulocochlear nerve. Neurostimulation rostral to the spiral ganglion has also been performed by De Ridder et al. using an electrode positioned at the auditory cortex (11;20). The advantages of these two methods of neurostimulation may be their more directly-applied stimulation of the auditory pathways, which might result in an increase in treatment success. They do not cause damage to the cochlea and might therefore be successful in still functional ears. Disadvantages may be the surgical risks such as haematoma, meningitis, CSF leakage and facial nerve damage.

Both pre- and post-spiral ganglion neurostimulation attempt to restore the afferent input to the auditory system. Whether neurostimulation of the vestibulocochlear nerve achieves the same results in hearing subjects needs to be investigated.

**Conclusions**

Long-term follow-up of neurostimulation treatment in chronic tinnitus sufferers shows promising results according to this pilot study. Long-term follow-up shows better results than follow-up after three months; the neurostimulation system apparently needs some time to achieve its effects. The reported reduction of tinnitus severity could not be objectified using tinnitus-specific audiometric tests. In none of the patients did the tinnitus disappear, instead it was replaced by another, pleasantly-perceived sound. This alteration of character explains the treatment success. The results of this study also proved the safety of this treatment since no long-lasting surgical risks or complications occurred and no side effects were noted during long-term evaluation. Further studies with neurostimulation are needed before accepting neurostimulation as a new treatment modality for chronic, therapeutically refractory tinnitus.

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Reference List