Cochlear implants

Bilateral implantation and future indications

Alice van Zon

Cover design by Mart Rozenbeek

The cover, which is double sided, represents binaural hearing and illustrates the enormous impact of sound perceived within the city. The inside of the cover shows the inner ear with a cochlear implant (courtesy of MED-EL Ltd). The patent for the first cochlear implantation is presented further inside.

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Cochlear implants

Bilateral implantation and future indications

Cochleaire implantaten
Bilaterale implantatie en toekomstige indicaties
(*met een samenvatting in het Nederlands*)

Proefschrift

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Alice van Zon
geboren op 21 augustus 1987
te Heerlen

Promotor:	Prof. dr. R.J. Stokroos
Copromotoren:	Dr. I. Stegeman Dr. G.A. van Zanten

‘Om innerlijke rust te vinden,
moet je afmaken waaraan je begonnen bent.’
Boeddha

CONTENT

PART TWO FUTURE INDICATIONS

CHAPTER

1

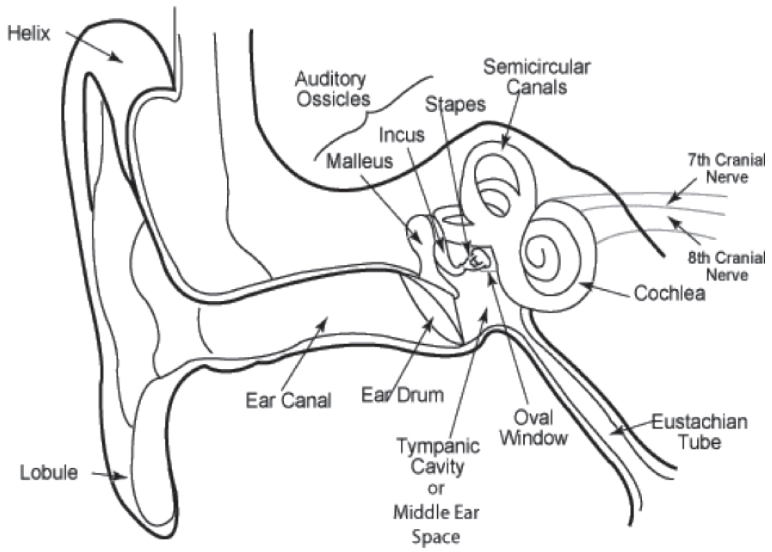
General introduction

1. Anatomy of the ear

The human ear is a complex sensory organ which comprises much more than the visible external part. The ear can be divided in three parts: the outer ear which consists the pinna and external auditory canal, the middle ear including the tympanic membrane and the three ossicles (malleus, incus, stapes) and the inner ear or cochlea (Figure 1).

The cochlea is a spiral-shaped cavity with circa two and a half turns around its axis (modiolus) in the osseous labyrinth and accommodates the membranous labyrinth. The membranous labyrinth contains three compartiments, or scalae, filled with fluid: the inner compartment or scala media containing endolymph and the outer compartments or scalae tympani and vestibuli containing perilymph (Figure 2). Both have different unique ionic compositions essential to regulate electrochemical signals.[1,2]

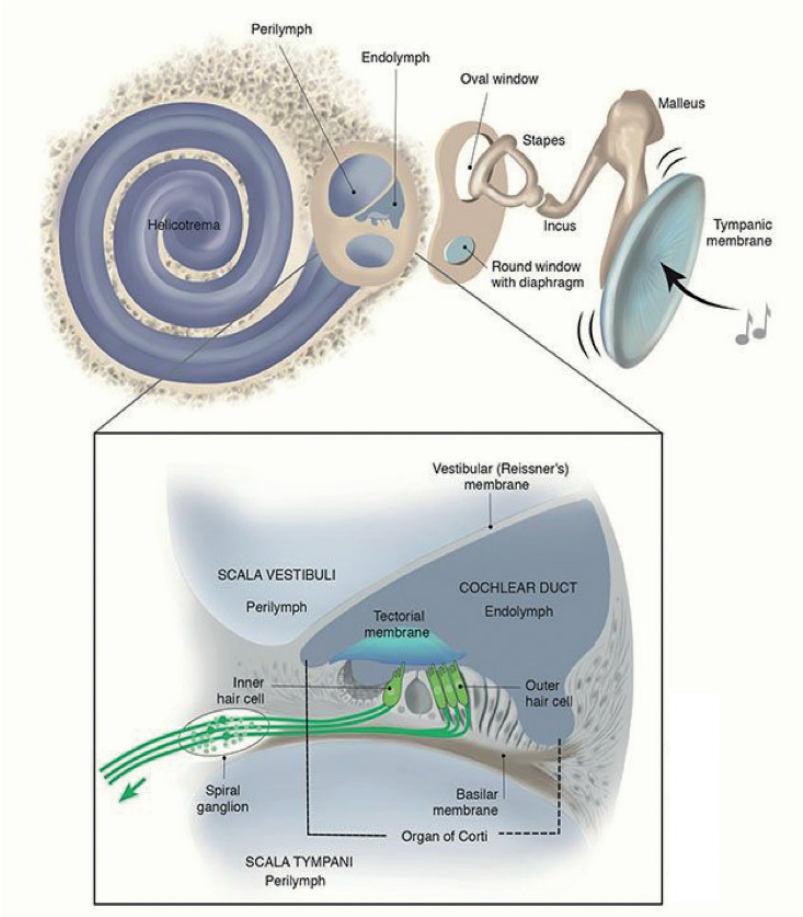
Figure 1. Anatomy of the human ear



2. Physiology of hearing

Sound pressure waves reach the outer ear and are transported through the external ear canal to reach the tympanic membrane. The tympanic membrane vibrates in response to sound pressure waves and passes on these vibrations to the malleus, incus and stapes respectively. The footplate of the stapes connects to the oval window of the cochlea, which causes the perilymph fluid of the scala vestibuli to move (Figure 2). As fluid is incompressible, the inward movement of the stapes footplates causes an outward movement of the elastic membrane of the round window (jeu des fenêtres).

Figure 2. Anatomy of the inner ear, including a longitudinal section through the modiolus of the cochlea
Cranial nerves 3th edition. © 2010 Wilson-Pauwels et al



At very low (inaudible) frequencies the vibrational pressure wave flows up the entire scala vestibuli through the apex and down the scale tympani to the round window. For higher frequencies the vibration passes through the cochlear duct at a place the closer to the stapes as the frequency is higher. At that position the sensory epithelium on the basilar membrane vibrates with the vibrating fluid; higher frequencies cause a motion at the base of the cochlea, which is narrower and stiffer, and lower frequencies at the apex, which is wider and more flexible, creating a topographical mapping of frequency called tonotopy (Figure 3). This tonotopical organization of the cochlea enables us to hear frequencies from 20 Hz to 20kHz.[2,3]

The basilar membrane supports the organ of Corti, which is composed of sensory hair cells (HCs). The HCs consist of one row of inner hair cells (IHCs) and three rows of outer hair cells (OHCs). The IHCs are the actual sensory receptors of sound pressure waves which convert the vibration of a sound into an electrical signal; fluid vibrations in the cochlea cause the stereocilia on the HCs to move and release electrochemical signals, after which the IHCs evoke action potentials in the spiral ganglion cells (SGCs) of the auditory nerve that in turn target the brainstem and auditory cortex to perceive sound. The OHCs actively amplify the vibration of the basilar membrane in order to improve hearing sensitivity.

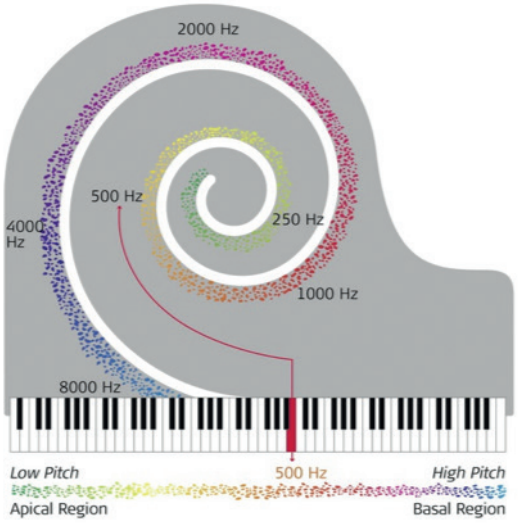


Figure 3. Tonotopy in the cochlea
Courtesy of Medel Ltd

3. Hearing loss

According to the World Health Organization (WHO), around 466 million people worldwide have disabling hearing loss (> 40dB loss in the better ear).[4] Hearing loss can be distinguished in conductive hearing loss and sensorineural hearing loss (SNHL). A conductive hearing loss makes it difficult for sounds to get to the inner ear due to problems in the outer or middle ear, but the fragile structures of the inner ear have remained intact. In most cases, a conductive hearing loss can be treated with either surgery or various types of hearing aids, depending on the etiology of the conductive loss. Unfortunately, the most common kind of hearing loss is SNHL. This is also the kind of hearing loss that is important to understand for current thesis. In SNHL the fragile HCs are damaged due to aging, overexposure to loud sounds, infectious diseases (e.g., rubella and meningitis), certain drugs or genetic defects. Mostly, SNHL is permanent and worsens with increasing age.[5]

Hearing loss can be categorized in five grades as described by the WHO.[6] Treatment options depend on the grade of impairment. In case of slight (26-40 dB) to moderate (41-60 dB) SNHL, HCs may still be there, but they may require the addition of hearing aids to amplify sounds and evoke action potentials in the SGCs for sound perception in the brain. When there is severe (61-80 dB) to profound (> 81dB) impairment, even the most powerful hearing aids may be inadequate. Since there is a lack of functional HCs, sounds may not be able to reach the auditory cortex at all. This is where cochlear implants come in.

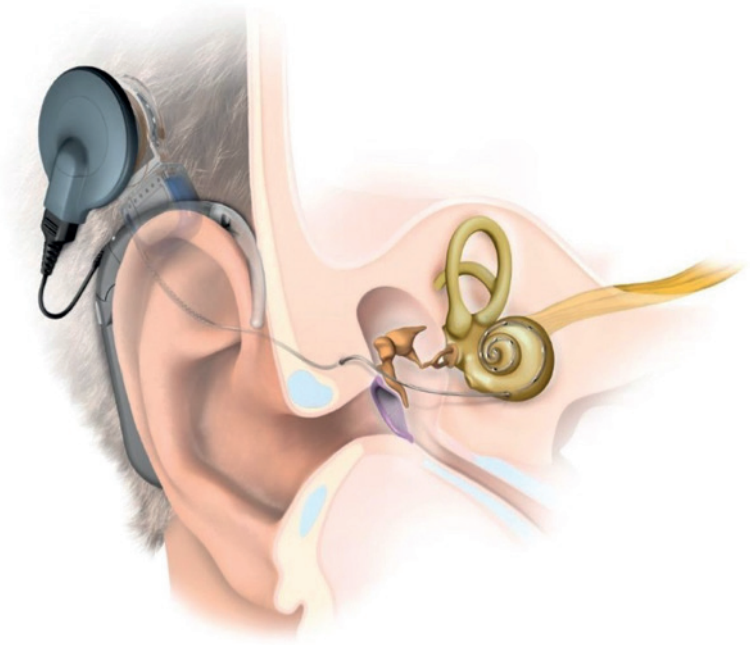
4. Cochlear implantation

A cochlear implant replaces the function of the cochlea by electrically stimulating the auditory nerve. A cochlear implant consists of an external part: a microphone, speech processor and transmitting coil, and an internal part: a receiver and electrode array (Figure 4). The microphone captures sound waves, which are converted to digital signals by the speech processor. This digital sound is led to the transmitter, which in turn transmits these signals to the subcutaneous receiver. When these signals are presented to the receiver, the signals are converted into electrical signal that is transferred to the electrode array within the cochlea. This way, SGCs in the auditory nerve are stimulated directly and thereby sound perception is restored.

The electrode array can be inserted all the way up through the scala tympani to the apex. This way, SGCs in specific regions can be stimulated by selectively using the contacts on the array. Since different pitches can be noticed through a cochlear implant, frequency tuning of the cochlea due to tonotopy can be restored to a certain degree.[7]

In 1961, William House and John Doyle implanted the first cochlear implant in Los Angeles.[8] In 1986, the first Dutch cochlear implant was placed in Utrecht. In the last decades, cochlear implantation (CI) has become a widely applied intervention in the treatment of patients with severe to profound SNHL when hearing aids are no longer effective. Currently, more than 300.000 people worldwide use cochlear implants to restore functional hearing.[9] The criteria for CI widen over time; audiological criteria for CI have been adapted from bilateral deafness (>110 dB SNHL) in the early 1980s, to severe hearing loss (>70 dB HL) in the 1990s, and nowadays a cochlear implant is usually provided when the speech perception in silence score with hearing aids is < 50% at 65dB (normal conversational speech level) and there is still some residual hearing.[10]

Figure 4. Schematic figure of a cochlear implant
Courtesy of Medel Ltd



5. Binaural hearing

Hearing with two ears, binaural hearing, has proven to be superior to unilateral hearing in both normal-hearing listeners and in those with binaural hearing aids.[11,12,13] The advantages of binaural hearing are based on three principles:

1. The squelch effect: the ability of the brain to exploit the noise coming to the ear closest to the noise in order to increase the signal to noise ratio (SNR) in the ear closest to the speech, speech perception in noise will be improved.[14,15]

2. The binaural summation effect: the ability of the auditory system to combine the information from both ears and to derive benefit from this combined information centrally leading to increased perceived loudness of sounds.[16]

3. The head shadow effect: the presence of the head results in differentiated SNRs between both ears due to differential filtering of sounds. This makes a subject able to attend to the ear with the most favorable SNR.[17]

Based on this knowledge, bilateral hearing aid fitting is reimbursed in the Netherlands for patients with bilateral hearing loss of at least 35dB in both ears and unilateral hearing aid fitting in case of unilateral hearing loss of at least 35dB in one ear.

6. Bilateral cochlear implantation

Interest in bilateral cochlear implantation (BiCI) for patients with severe to profound SNHL has been growing over the last decade. Although cochlear implant users achieve high levels of spoken word recognition when speech is presented in quiet, even the most successful users still experience difficulty in the presence of competing sounds and are poor at identifying the localization of sounds.[18]

The additional benefit of a hearing aid in the contralateral ear is limited in patients with less or even no residual hearing.[19] Several studies demonstrated that BiCI compared to unilateral cochlear implantation (UCI) is beneficial when speech perception in noise and localization capabilities are concerned.

However, they also emphasize that there is a lack of high-quality studies.[18] Therefore, till date, Dutch insurance companies do not provide reimbursement for a second cochlear implant. BiCI is only reimbursed when deafness is caused by meningitis, which may lead to ossification of the cochlea, or in case of deaf-blindness. For most children with severe to profound SNHL, bilateral implantation has become standard care.[20]

7. Future indications for cochlear implantation

Surgical techniques for CI has improved over the last three decades, which has increased the utility and safety of CI. As a result, the criteria for CI has broadened during the last years; cochlear implants are now approved in bilateral hearing impaired patients with residual hearing.[21] It is expected that CI will also be an acceptable treatment for other indications in the near future. Besides BiCI, in this thesis we will also focus on the relation between CI and tinnitus and CI as a treatment for unilateral deafness.

7.1. Cochlear implantation and tinnitus

Tinnitus is a disturbing phenomenon defined as an acoustic sensation in the absence of an external sound.[22] Tinnitus can be classified into objective and subjective tinnitus. Objective tinnitus is generated in the body and is audible for both the patient and the examiner (e.g., myoclonic contractions or neurovascular conflicts). Subjective tinnitus is the most common type of tinnitus which is only audible for the patient and does not have a specific sound source within the body. [23] In current thesis, we will only focus on patients with subjective tinnitus.

Subjective tinnitus is a common problem in adults with a prevalence ranging from 10% to 15%. Prevalence increases with age and an even stronger association is seen between tinnitus and SNHL, reaching a prevalence of 67% to 86% in cochlear implant candidates.[24,25] In some people, the effect of tinnitus has a significant negative impact on quality of life (QoL) and therefore needs attention.

There are different theories about the mechanisms involved in the onset of tinnitus, but the exact underlying pathophysiology still remains unclear. Initially, it was hypothesized that tinnitus had a peripheral cause, located in either the cochlea or auditory nerve. More recent studies hypothesize that the

induction of tinnitus could be a result of changes in neural activity in the central auditory systems directly related to SNHL which causes either reorganization of the topographical mapping in the cochlea or an imbalance of excitatory and inhibitory inputs transferred to the central auditory system.[23] However, the association between SNHL and tinnitus is also subject of discussion, not all patients with SNHL experience tinnitus and conversely normal hearing patients may have tinnitus. This makes the understanding of the pathophysiology of tinnitus even more difficult.[26]

Till now, there is no standard procedure for the management of tinnitus. Therapy mostly consist of psychological therapy, including cognitive behavioral therapy and tinnitus retraining therapy, to support coping and improve habituation to the tinnitus. In case of hearing loss, also sound enrichment with hearing aids and tinnitus maskers is part of the treatment. This becomes impossible in patients with profound SNHL or complete deafness.[23]

Already in 1981, House and Brackmann described a suppressive effect of CI on tinnitus.[27] The last years more studies investigated this phenomenon; suppression rates of tinnitus after CI vary widely from 8% to 61% and rates for a decrease in tinnitus are even higher and vary from 64% to 100%.[28-33] Nevertheless, an increase of tinnitus or even induction of tinnitus in 1% to 5% is also described.[34,35]

7.2. Cochlear implantation and single-sided deafness

In single-sided deafness (SSD) an individual has normal hearing in one ear and impaired hearing in the other ear. As explained earlier in this introduction, binaural hearing provides important benefits to normal hearing people. Patients with SSD become aware of the importance of binaural hearing in their daily life in terms of social interaction and communication.[36]

Current treatment options for patients with SSD consist of hearing improvement with either a Contralateral Routing of Signal (CROS) with help of a wired or wireless microphone on the hearing impaired ear of a conventional hearing aid on the better ear, or a Bone Conduction Device (BCD) at the hearing impaired side. A BCD conducts sound from the hearing impaired side by vibration of the skull bone and stimulates the cochlea from the better ear directly. Both devices address the head shadow effect to a certain degree, but they are not able to restore actual binaural hearing.

The limitations of CROS or BCD may be overcome by CI. Promising results regarding speech perception in noise and sound localization in patients with SSD haven been reported.[37] Next to these audiological benefits, CI may also result in reduction of tinnitus in this group.[38]

8. Aims and outline of this thesis

This thesis is divided in two parts. The first part of the thesis focusses on the benefits of BiCI compared to UCI. In the second part of the thesis we will focus on potential future indications for CI.

PART ONE – BILATERAL COCHLEAR IMPLANTATION

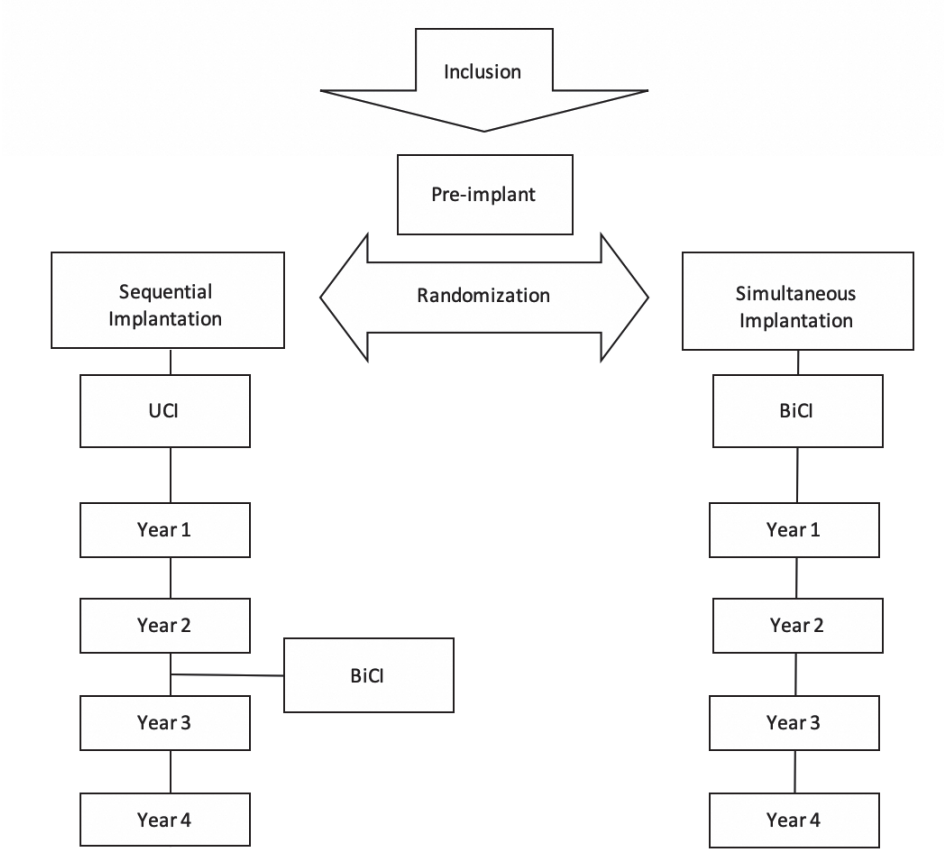
In 2010, we started a multicenter randomized controlled multicenter trial on the benefits of BiCI compared to UCI in adults with severe bilateral postlingual SNHL. Thirty-eight patients were randomly allocated to either simultaneous BiCI or sequential BiCI. The 19 patients in the sequential group first received one cochlear implant and after 2 years they received their second cochlear implant. A flowchart of the study is presented in Figure 5. **Chapter 2** describes the first results of this RCT in which UCI was compared to BiCI after 1-year of follow-up. In **chapter 3** we evaluated the results after 2-years of follow-up and discuss a possible learning effect of cochlear implant users over time. **Chapter 4** investigates if a squelch effect occurs after simultaneous BiCI. **Chapter 5** evaluates the accuracy of an often used test method by answering the question if simulated unilateral hearing (switching off one cochlear implant) results in the same outcomes as real life unilateral hearing with one cochlear implant and a non-implanted contralateral ear.

PART TWO – FUTURE INDICATIONS

In **chapter 6** we systematically reviewed the literature concerning the effect of UCI on tinnitus in patients with profound to severe bilateral SNHL. As part of the RCT discussed in the first part of this this, in **chapter 7** we performed a prospective study in which we evaluated the effect of both UCI and BiCI on tinnitus in patients with severe bilateral postlingual SNHL. **Chapter 8** describes

a systematic review concerning the clinical outcome of CI for patients with SSD or asymmetrical hearing loss (AHL).

Figure 5. Flowchart of RCT comparing simultaneous BiCI to UCI or sequential BiCI



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PART

ONE

BILATERAL COCHLEAR IMPLANTATION

CHAPTER

2

Comparison of bilateral and unilateral cochlear implantation in adults: a randomized controlled trial

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JAMA Otolaryngol Head Neck Surg. 2016 Mar;142(3):249-56.

ABSTRACT

Importance

The cost of bilateral cochlear implantation (BiCI) is usually not reimbursed by insurance companies because of a lack of well-designed studies reporting the benefits of a second cochlear implant.

Objective

To determine the benefits of simultaneous BiCI compared with unilateral cochlear implantation (UCI) in adults with postlingual deafness.

Design, setting and participants

A multicenter randomized clinical trial (RCT) was performed. The study took place in five Dutch tertiary referral centers: the University Medical Centers of Utrecht, Maastricht, Groningen, Leiden, and Nijmegen. Forty patients eligible for cochlear implantation (CI) met the study criteria and were included from January 12, 2010, through November 2, 2012. The main inclusion criteria were postlingual onset of hearing loss, age of 18 to 70 years, duration of hearing loss of less than 20 years, and a marginal hearing aid benefit. Two participants withdrew from the study before implantation. Nineteen participants were randomized to undergo UCI and 19 to undergo BiCI.

Interventions

The BiCI group received two cochlear implants during one surgery. The UCI group received one cochlear implant.

Main outcomes and measures

The primary outcome was the Utrecht Sentence Test with Adaptive Randomized Roving levels (speech in noise, both presented from straight ahead). Secondary outcomes were consonant-nucleus-consonant (CNC) words in silence, speech-intelligibility test with spatially separated sources (speech in noise from different directions), sound localization, and quality of hearing questionnaires. Before any data were collected, the hypothesis was that the BiCI group would perform better on the objective and subjective tests that concerned speech intelligibility in noise and spatial hearing.

Results

Thirty-eight patients were included in the study. Fifteen patients in the BiCI group used hearing aids before implantation compared with 19 in the UCI group. Otherwise, there were no significant differences between the groups' baseline characteristics. At 1-year follow-up, there were no significant differences between groups on the Utrecht Sentence Test with Adaptive Randomized Roving levels (9.1 dB, UCI group; 8.2 dB, BiCI group; P =0.39) or the CNC test (median percentage correct score 85.0% in the UCI group and 86.8% in the BiCI group; *P* = 0.21). The BiCI group performed significantly better than the UCI group when noise came from different directions (median speech reception threshold in noise, 14.4 dB, BiCI group; 5.6 dB, BiCI group; *P* 0<.001). The BiCI group was better able to localize sounds (median correct score of 50.0% at 60°, UCI group; 96.7%, BiCI group; *P* <0.001). These results were consistent with the patients' self-reported hearing capabilities.

Conclusions and relevance

This RCT demonstrates a significant benefit of simultaneous BiCI above UCI in daily listening situations for adults with postlingual deafness.

INTRODUCTION

More than 550 million people worldwide have disabling hearing loss (pure-tone average [PTA] at 500, 1000, and 2000Hz, ≥35dB hearing level in the better ear). More than 60 million have severe hearing loss or worse (PTA, ≥65dB hearing level).[1] For the latter group, a cochlear implant may be provided. Cochlear implantation (CI) has proven to be very successful, especially for patients who have well-developed central auditory pathways (i.e., in those who received an implant at an early age or who lost their hearing later in life after auditory cortex development).[2] In the Netherlands, CI is considered a treatment option if hearing aids do not provide sufficient benefit. This means that the aided speech perception threshold in quiet, and the phoneme score, measured with consonant-nucleus-consonant (CNC) words, is 50% or less at a 65dB sound pressure level (SPL). Since 2012, bilateral cochlear implantation (BiCI) has been standard care for children in the Netherlands until the age of 5 years. Adults only receive reimbursement for a second implant when deafness is caused by meningitis, which may lead to ossification of the cochlea. There is an ongoing discussion in the Netherlands about whether BiCI should be standard care for adults, as it is in Germany and Scandinavia.[3]

Binaural hearing enables one to differentiate sounds of interest from background noise and locate where sounds come from by using different effects of binaural hearing: head shadow, squelch, and summation.[4-7] Several reviewers have analyzed the benefits of BiCI compared with unilateral cochlear implantation (UCI). BiCI seems beneficial for speech perception in noise, localization of sounds, and improvement of quality of hearing and quality of life; however, reviewers conclude that most studies have a low level of evidence.[8-10] For this reason, Dutch insurance companies have decided that reimbursement of a second cochlear implant in adults cannot be justified.

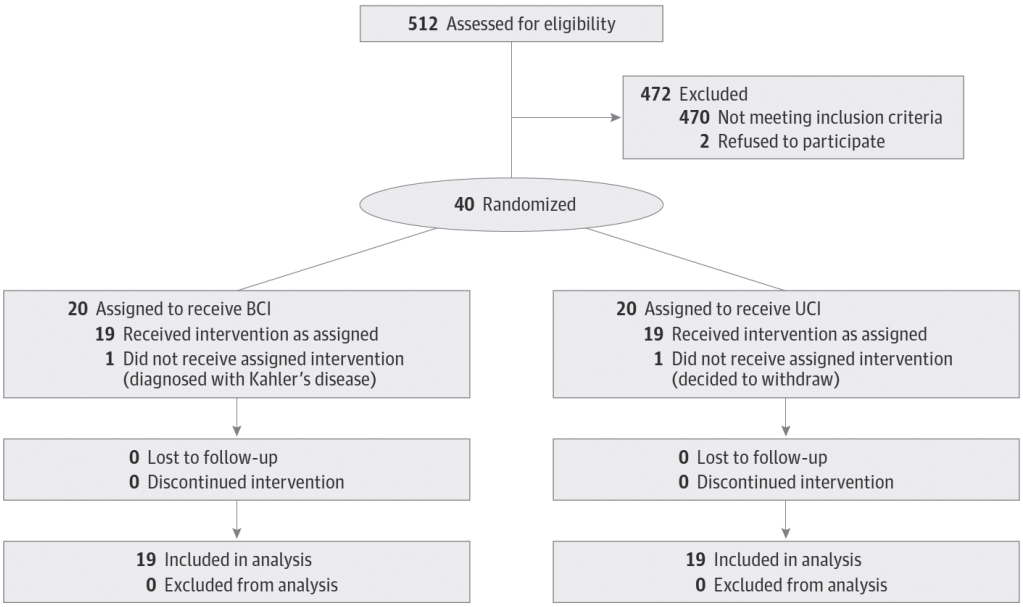
In this article, we present the results of a multicenter randomized clinical trial (RCT) on the benefits of simultaneous BiCI compared with UCI in adults with severe bilateral postlingual hearing loss. We present objective hearing test results for hearing in noise and quiet, which also includes sound localization capabilities, and patients' self-reported quality of hearing results.

METHODS

Trial design and participants

In the Netherlands, CI is performed in eight tertiary referral centers, five of which participated in this RCT: the University Medical Centers of Utrecht, Maastricht, Nijmegen, Leiden, and Groningen. The study criteria were verified for each patient eligible for CI, in the multidisciplinary CI teams, from January 12, 2010, through November 2, 2012 (Figure 1). The inclusion criteria were as follows: 1) age of 18 to 70 years; 2) postlingual onset of hearing loss (participants attended mainstream education); 3) duration of severe to profound hearing loss of less than 20 years in each ear and a difference in duration of hearing loss between the two ears of less than 10 years; 4) marginal hearing aid benefit, defined as an aided phoneme score less than 50% at a 65dB SPL; 5) Dutch as native language; 6) willingness and ability to participate in all scheduled procedures outlined in the protocol; 7) general health allowing general anesthesia for the duration of potential simultaneous BiCI; 8) Dutch health insurance coverage; and 9) agreement to undergo implantation with Advanced Bionics implants. Exclusion criteria were as follows: 1) previous CI; 2) disability that could interfere with the completion of the tests; 3) abnormal cochlear anatomy in one or both ears; and 4) chronic ear infection in one or both ears. The criteria were double-checked by the main investigators in Utrecht before a patient received written information from his or her otolaryngologist and was asked to participate in the study. Baseline hearing tests were performed as part of the standard CI workup and were equal in all centers. They encompassed standard pure-tone audiometry and speech intelligibility in quiet, with and without hearing aids, using standard CNC words. After patients provided written informed consent, self-reported questionnaires on hearing were filled out at the patients' own hospitals before participants were randomly allocated to one of two treatment groups. This order was chosen because the knowledge of receiving one or two implants could influence the participant's answers and bias the results.

Figure 1. Flowchart of enrollment



This flowchart shows the number of patients eligible for cochlear implantation in whom study criteria were assessed. The participants were randomly allocated to unilateral cochlear implantation (UCI) or bilateral cochlear implantation (BCI). All were available for follow-up.

Randomization and masking

The participants were randomized to undergo UCI or simultaneous BiCI. The randomization program was designed by an independent data manager and could not be influenced by any of the researchers. We used a block randomization per center strategy to obtain an equal distribution between UCI and BiCI in all centers. Masking was not possible because of the nature of the study; one could see on the outside whether a patient had one or two implants. This study was approved by the human ethics committees of all participating centers and was conducted according to the principles expressed in the Declaration of Helsinki.

Unavailable for follow-up

One participant, who was randomized to the BiCI group, was excluded when diagnosed as having Kahler's disease only a few weeks later (Kahler's disease or multiple myeloma is a cancer in which antibody-producing plasma cells grow

in an uncontrolled and invasive [malignant] manner). Another participant, who was randomized to the UCI group, decided to withdraw when his surgery was postponed because of a temporary recall of Advanced Bionics implants. These participants were replaced by new participants. All other patients completed the test sessions for the 1-year follow-up period (Figure 1).

Study procedures

All participants received HiRes90K cochlear implants (Advanced Bionics) to ensure that they had access to the same technology. In the UCI group, patients chose the ear of implantation, which was usually the ear with the worst hearing. They were allowed to discuss their decision with members of the CI team but made the choice themselves. Because the objective of the study was to compare BiCI with the next best alternative, the use of a contralateral hearing aid was encouraged in the UCI group. The surgery and rehabilitation took place in the patients' own hospital, and rehabilitation started approximately 6 weeks after surgery. The implant processing strategy was defined in a protocol for all centers. All patients were fitted with Harmony processors (Advanced Bionics) except for two (one in each group) who used Neptune processors (that have an identical processing strategy but a body-worn microphone). Four weeks before testing, they switched to Harmony processors to allow time for acclimatization. All tests were performed with the patients wearing Harmony processors.

Test procedures at 1-year follow-up

One year after surgery all participants were asked to complete the quality of hearing questionnaires for the second time. Further spatial hearing tests were performed at the University Medical Center Utrecht by four well-trained researchers (Y.E.S., A.v.Z., and A.B.R.) who strictly followed the same protocol. All gathered data were double-checked by an independent person who did not have any other connections to the otorhinolaryngology department.

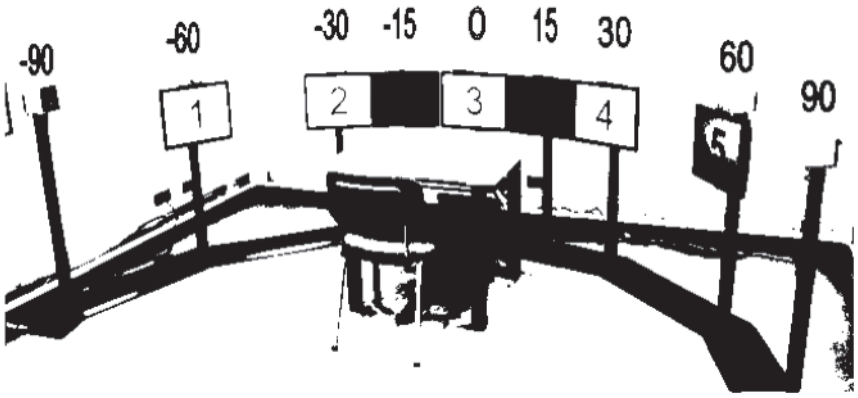
The Dutch AB-York crescent of sound

Speech intelligibility in noise and localization capabilities were tested with the Dutch AB-York crescent of sound.[11,12] The test battery included the following: 1) Utrecht - Sentence Test with Adaptive Randomized Roving levels (U-STARR), 2) speech intelligibility test with spatially separated sources (SISSS), and 3) a sound localization test. The AB-York crescent of sound contains nine audiovisual stands, seven positioned at 30° intervals and two at 15° intervals on either side of 0° (Figure 2). In the U-STARR, Dutch VU-98 sentences were presented at a 65, 70,

or 75dB SPL (randomly selected), both speech and noise coming from straight ahead. The number of keywords correctly repeated per sentence was scored. Sentences were presented with an initial signal to noise ratio (SNR) of +20 dB (sentence 20 dB louder than noise). If a sentence was scored as correct, the SNR for the next sentence was decreased by increasing the noise level. If a sentence was scored as incorrect, the SNR was increased. The SNR was changed with consecutive steps of 10, 5, and 2.5 dB. The mean SNR of the last ten sentences was calculated, which resulted in the speech reception threshold in noise. For the SISSS, the same procedure was used as for the U-STARR. The only difference was that the sentences were presented from 60° to the left (–60° azimuth) or to the right (+60° azimuth) of the patient. For the sound localization test, numbers were shown on screens, representing the loudspeakers above them. A phrase was presented from one of the loudspeakers (randomly at a 60, 65, or 70dB SPL), 30 times in total. The results were percentage of correct responses with 60°, 30°, and 15° angles between speakers. All tests were performed monaurally, with either one of the cochlear implants or the hearing aid switched on; bilaterally, using both cochlear implants; or bimodally, with both the cochlear implant and hearing aid switched on. Participants were instructed to face the loudspeaker positioned in front of them and not to turn their head during the tests.

To compare BICI to the next best option, we defined a patient's preferred situation for each patient in the UCI group. This was the daily hearing situation: either wearing the cochlear implant only or wearing a cochlear implant and hearing aid. Results from the BCI group were compared with results of the patient's preferred situations from the UCI group. When speech and noise come from different directions, one is best able to understand the speech when it is presented to the best-hearing ear and noise to the worst-hearing ear. In the UCI group, this situation occurs when speech is presented to the cochlear implant side and noise to the contralateral side. Patients who underwent bilateral implantation generally also have one side with which they hear better than with the other. Per participant, we defined this as the best hearing situation and the worst hearing situation. The latter occurs when speech is presented to the worst-hearing side and noise to the best-hearing side.

Figure 2. The AB-York crescent of sound test setup



This setup was used to conduct the Utrecht Sentence Test with Adaptive Randomized Roving levels, speech intelligibility test with spatially separated sources, and localization tests. The numbers on the screens represent the answer options, and the numbers above the speakers represent degrees of angle.

Outcomes

The primary outcome was the U-STARR. Secondary outcomes were the SISSS, CNC words in quiet, sound localization, and self-reported benefits in everyday listening situations assessed with the Speech, Spatial, and Qualities Hearing Scale (SSQ),[13] Time Trade-off (TTO),[14] a visual analog scale (VAS) for hearing (scale of 0-100), and Nijmegen Cochlear Implant Questionnaire (NCIQ).[15] On the TTO, participants were asked how many life-years they were willing to give up to live the rest of their lives with perfect hearing. (TTO = [(Life Expectancy – Amount of Years to Give Up for Perfect Hearing)/Life Expectancy] × 100).[14] This question needs good instruction; therefore, we decided not to let patients answer it in their own hospitals preoperatively, but we asked them personally at the 1-year follow-up test moment at the University Medical Center Utrecht.

Sample size calculation

To detect a clinically relevant difference of 3 dB in the SNR between groups on the hearing in noise test and a standard deviation (SD) of 3 dB, with an α of 0.05 and a power of 80%, we calculated that 14 patients per group were needed. To compensate for any data unavailable for follow-up, five additional patients were included in each group. Three decibels is the magnitude of the summation effect that is typically observed.

Statistical analysis

To compare baseline characteristics and preoperative test results, we used the *t* test for numeric, normally distributed data and the χ2 test for ordinal data. None of the postoperative test results were normally distributed. We therefore present median outcomes and ranges. We used the Mann-Whitney tests for all hearing test results (TTO, VAS, and SSQ) for comparing UCI and BiCI data. For the NCIQ, we used the χ2 test. To compare preoperative with postoperative findings, we used the Wilcoxon signed-rank test. To analyze whether residual hearing had an effect on the outcomes, we calculated Spearman ρ correlation coefficients between the preoperative maximum CNC score (with or without hearing aid) and the U-STARR, SISSS, and localization test results. To make it easier to compare our findings with the literature, in which means (SDs) are usually presented, we added means (SDs).

RESULTS

Patient characteristics and objective results

The baseline characteristics of the 38 included patients are summarized in Table 1. Fifteen patients in the BiCI group used hearing aids before implantation compared with 19 in the UCI group. Otherwise, no significant differences were found between the groups' baseline characteristics. One year after implantation, hearing had clearly improved in both groups compared with the preoperative situation (Table 2). Although no significant differences were found between groups on the U-STARR and CNC test, clear differences appeared when sounds came from different directions. When speech was presented to the ear without an implant and noise to the ear with an implant (worst hearing situation), the patients who underwent UCI performed significantly worse than the patients who underwent BiCI in their worst hearing situations on the SISSS. Patients who underwent BiCI had significantly better results on all localization tests (Table 2).

Residual hearing

In the UCI group, seven of 19 patients did not use a contralateral hearing aid at 1-year follow-up because they did not experience any benefits from it (Table 2). The objective test outcomes did not correlate significantly with the preoperative maximum CNC score with hearing aid (n = 12) (U-STARR: $P = 0.60$, SISSS: $P = 0.24$, localization tests at 15°, 30° and 60°: $P = 0.42$, $P = 0.78$, $P = 0.64$,) or without hearing aid (n = 7) (U-STARR: $P = 0.29$, SISSS: $P = 0.09$, localization

tests at 15°, 30° and 60°: $P = 0.17$, $P = 0.59$, $P = 0.29$), which means that residual hearing did not influence the results.

Table 1. Patient characteristics

Characteristics	UCI (n=19)	BiCI (n=19)
Gender, male:female	11:8	8:11
Age in years at CI	52.5 (12.5) [26-67]	47.8 (15.9) [18-70]
Age in years at onset of severe hearing loss		
Right ear	30.5 (20.1) [3-55]	30.5 (17.2) [3-63]
Left ear	30.6 (19.8) [3-55]	30.0 (17.5) [3-63]
PTA (dB)		
Right ear	106 (12) [78-125]	106 (16) [80-130]
Left ear	108 (13) [83-127]	108 (18) [77-130]
Maximum phoneme score (%)	46.2 (20.4) [0-80]	42.1 (27.6) [0-90]
Treatment hospital		
Utrecht	11	8
Maastricht	4	5
Nijmegen	2	3
Leiden	1	2
Groningen	1	1
Hearing aid use before CI		
Yes	19	15
No	0	4
Cause of deafness		
Hereditary	7	9
Unknown and progressive	9	6
Sudden Deafness	0	2
Head trauma	0	1
Meningitis	2	0
Rhesus antagonism	1	0
Sound exposure	0	1

Data are presented as mean (standard deviation) [range].
Abbreviations: BiCI, bilateral cochlear implantation; CI, cochlear implantation; PTA, pure-tone audiometry (average at 0.5, 1, and 2kHz); UCI, unilateral cochlear implantation.

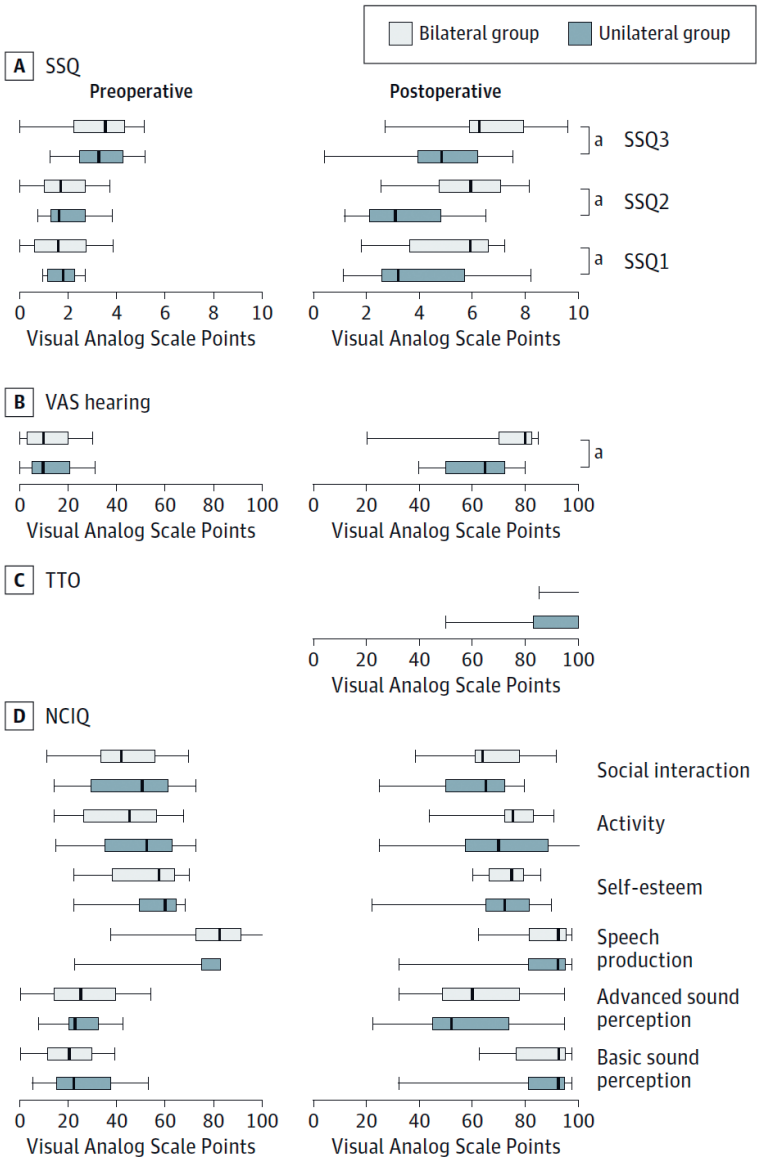
Table 2. Objective 1-year postoperative outcomes

		Patient preferred situation (with or without HA)		
		UCI (n=19)	**BCI (n=19)**	***P* value**
Residual hearing in the ear without an implant (phoneme score in silence, % CNC words)				
HA users (n=12)	Mean (SD)	22.7 (22.7)	…	…
	Median [range]	22.5 [0-65]	…	…
Non HA users (n=7)	Mean (SD)	8.3(21.9)	…	…
	Median [range]	0 [0-58]	…	…
Whole UCI group	Mean (SD)	17.4 (23.0)	…	…
	Median [range]	0 [0-65]	…	…
Speech in noise and in silence				
Speech in noise both from straight ahead, (SRTn in dB)	Mean (SD)	10.0 (6.3)	8.2 (5.3)	
	Median [range]	9.1 [2.2-30]	8.2 [0.3-18.4]	0.39
Phoneme score in silence (% CNC)	Mean (SD)	83.4 (8.9)	86.8 (9.5)	
	Median [range]	85.0 [70-98]	88.0 [67-100]	0.21
Speech and noise from different directions SISS performing situation (SRTn in dB)				
Best	Mean (SD)	5.9 (7.3)	4.1 (5.9)	
	Median [range]	5.0 [-3.1-30.0]	4.1 [-4.7-14.1]	0.61
Worst	Mean (SD)	15.8 (6.3)	7.1 (7.5)	
	Median [range]	14.4 [8.1-30.0]	5.6 [-2.8-22.8]	<0.01*
Localization of sounds (% correct)				
60°	Mean (SD)	50.5 (16.5)	93.7 (7.8)	
	Median [range]	50.0 [30.0-90.0]	96.7 [73.3-100.0]	<0.01*
30°	Mean (SD)	30.9 (10.2)	71.8 (14.0)	
	Median [range]	30.0 [16.7-50.0]	76.7 [43.3-96.7]	<0.01*
15°	Mean (SD)	29.0 (8.8)	56.7 (16.3)	
	Median [range]	30.0 [20.0-50.0]	53.3 [33.3-90.0]	<0.01*

Abbreviations: CNC, consonant-nucleus-consonant words; BiCI, bilateral cochlear implantation; HA, hearing aid; SISSSS, speech in spatially separated sources; SRTn, speech reception threshold in noise; UCI, unilateral cochlear implantation. Ellipses indicate date not applicable.

* *Significant at P < 0.05.*

Figure 3. Quality of hearing questionnaires



Preoperative and 1-year postoperative results on three quality of hearing questionnaires in 19 patients in the unilateral cochlear implantation group and 19 in the bilateral cochlear implantation group are shown. Abbreviations: NCIQ, Nijmegen Cochlear Implant Questionnaire; SSQ, Speech, Spatial and Qualities Hearing Scale; SSQ 1, speech understanding in silence, in background noise, resonating environments and on the phone; SSQ 2, spatial listening; SSQ 3, quality of hearing; TTO, time trade off; VAS, visual analog scale.

[*] *Significant difference at $P < 0.05$.*

Subjective results

No differences between the UCI and BiCI group on the quality of hearing questionnaire results (SSQ, VAS on hearing, and NCIQ) were found preoperatively (Figure 3). All participants reported significant improvement on all questionnaires at 1 year postoperatively. At 1-year follow-up, the BiCI group had significantly better results on the three chapters of the SSQ, VAS on hearing, and TTO than the UCI group. On the NCIQ, the BiCI group reported better hearing capabilities than the UCI group but not significantly so (social interaction: $P = 0.17$; activity: $P = 0.40$; self-esteem: $P = 0.25$; speech production: $P = 0.52$; advanced sound perception: $P = 0.14$; basic sound perception: $P = 0.60$) (Figure 3).

DISCUSSION

We present the results of the first RCT, to our knowledge, to investigate the benefits of simultaneous BiCI compared with UCI in adults with postlingual deafness. In quiet or when sound was presented to the ear with an implant, patients in the UCI group performed equally well as those in the BiCI group. However, in everyday life, sounds come from different directions, and there is usually background noise present. Our study reveals that patients undergoing BiCI significantly benefit from their second implant in these situations.

Comparison with the literature

Most studies published on the potential benefits of BiCI vs UCI are nonrandomized cohort studies, and often, patients who underwent BiCI were asked to deactivate one implant to assess differences between unilateral and bilateral hearing. This is not representative of actual UCI because the patients were used to listening with two implants in daily life. In addition, implantation would have caused insertion damage to the cochlea, deteriorating residual hearing.[8] As in our study, prior studies[16-19] found that bilateral implantation did not improve speech in noise understanding when both were presented from straight ahead,[16-18] although a summation effect has occasionally been found.[19] Dunnet al. assessed speech perception in noise, from separated sources, on 60 matched patients, who had undergone simultaneous BiCI or UCI.[20] As in our study, the former performed better than the latter. In our study, the patients in the BiCI group were able to localize sounds, which was difficult for the UCI group. Several other studies have found that bilateral implantation

makes sound localization possible.[18,21-25] The quality of hearing questionnaire results confirmed the objective findings. The BCI group evaluated their own performance in difficult listening situations, as represented in the SSQ, better than the UCI group. They also evaluated their overall hearing as better on the VAS. As in our study, Summerfield et al. reported a significant positive effect of a second cochlear implant in 24 UCI users on the SSQ.[26] Noble and colleagues compared 70 patients fit with one implant and 36 patients fit with bilateral implants (31 simultaneously and five sequentially) and also reported significantly better results in the BiCI group on the SSQ.[23] On the TTO, our two study groups had comparable results, which were similar to the results of Kuthubutheen et al.[27] On the NCIQ, Hinderink et al. reported comparable findings of 47 patients with postlingual deafness who underwent UCI.[15] To our knowledge, there is no literature on NCIQ results in patients undergoing BiCI. Of interest, no differences were found between the UCI and BiCI groups on the NCIQ. All participants had developed speech before losing their hearing, which explains the lack of difference on this subdomain within and between groups. A second implant apparently did not have an additional value on changes in the patients' self-esteem, activity levels, or social interactions. The NCIQ contains questions on hearing in easy and difficult situations but does not focus on spatial hearing like the SSQ does. This might explain why the results in the BiCI group are better but not significantly so.

Strengths and weaknesses

The major strength of our study was that allocation bias was minimized by using an RCT. Furthermore, the study group was homogeneous by setting strict inclusion and exclusion criteria, and none of the patients was unavailable for follow-up after having undergone implantation. In the UCI group, the contralateral cochlea was untreated, and most patients used a hearing aid to exploit that ear's even minimal function. We tested the participants after 1 year of implantation experience, which gave the brain time to adapt to this listening situation. Possible weaknesses of our study were that the patients were treated in five different centers and the included numbers of patients per center varied. We attempted to minimize this potential bias by using a per center block randomization strategy. Furthermore, the researchers and caregivers were not masked. However, we used a strict test protocol to minimize differences in testing among researchers.

CONCLUSIONS

This is the first report, to our knowledge, of an RCT reporting the benefits of simultaneous BiCI over UCI in adults in various listening situations. Although a second cochlear implant did not have an additional value in easy listening conditions, patients who underwent BiCI had significantly better hearing results when sounds came from different directions, such as in everyday noisy environments. This finding was demonstrated with objective hearing test results that were consistent with the participants' self-reported hearing capabilities.

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CHAPTER

3

Stable benefits of bilateral over unilateral cochlear implantation after two years: a randomized controlled trial

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ABSTRACT

Objective

To investigate hearing capabilities and self-reported benefits of simultaneous bilateral cochlear implantation (BiCI) compared with unilateral cochlear implantation (UCI) after a 2-year follow-up and to evaluate the learning effect of cochlear implantees over time.

Study design

Multicenter randomized controlled trial (RCT).

Methods

Thirty-eight postlingually deafened adults were included in this study and randomly allocated to either UCI or simultaneous BiCI. Our primary outcome was speech intelligibility in noise, with speech and noise coming from straight ahead (Utrecht Sentence Test with Adaptive Randomized Roving levels). Secondary outcomes were speech intelligibility in noise with spatially separated sources (SISSS), speech intelligibility in silence (Dutch phoneme test), localization capabilities and self-reported benefits assessed with different quality of hearing and quality of life (QoL) questionnaires. This article describes the results after 2 years of follow-up.

Results

We found comparable results for the UCI and simultaneous BiCI group, when speech and noise were both presented from straight ahead. Patients in the BiCI group performed significantly better than patients in the UCI group, when speech and noise came from different directions ($P = 0.01$). Furthermore, their localization capabilities were significantly better. These results were consistent with patients' self-reported hearing capabilities, but not with the questionnaires regarding QoL. We found no significant differences on any of the subjective and objective reported outcomes between the 1-year and 2-year follow-up.

Conclusions

This study demonstrates important benefits of simultaneous BiCI compared with UCI that remain stable over time. Bilaterally implanted patients benefit significantly in difficult everyday listening situations such as when speech and noise come from different directions. Furthermore, bilaterally implanted patients are able to localize sounds, which is impossible for unilaterally implanted patients.

INTRODUCTION

In the last decades, cochlear implantation (CI) has become a widely applied intervention in the treatment of patients with severe to profound bilateral sensorineural hearing loss (SNHL).

Although many patients with an unilateral cochlear implant achieve high levels of spoken word recognition when speech is presented in quiet, even the most successful users still experience difficulty in the presence of competing sounds and are poor at identifying the localization of sounds.[1] Hearing with two ears, binaural hearing, has proven to be superior to unilateral hearing in both normal hearing listeners and in those with binaural hearing aids.[2-4] The advantages of binaural hearing are based on three principles: 1) the squelch effect (ability of the brain to exploit the noise coming to the ear closest to the noise in order to increase the signal to noise ratio (SNR) in the ear closest to the speech)[5,6] , 2) the binaural summation effect (redundancy of auditory input)[7], and 3) the head shadow effect (resulting in a better SNR in one ear).[8] Based on this knowledge, hearing impaired patients usually receive two hearing aids. However, when hearing aids do not provide sufficient benefit (i.e., the aided speech perception threshold in silence is 50% or less at 65dB sound pressure level), it is standard clinical practice to provide only one cochlear implant in the Netherlands for adults. Several authors highlighted the lack of high-quality studies with a representative duration of follow-up concerning the additional effectiveness of bilateral cochlear implantation (BiCI) to unilateral cochlear implantation (UCI).[1,9-11] For this reason, Dutch insurance companies do not provide reimbursement for a second implant in adults.

Previously, our research group presented the results of the first randomized controlled trial (RCT) concerning the effectiveness of simultaneous BiCI compared with UCI after a 1-year follow-up.[12,13] This RCT demonstrates that there is a significant benefit of simultaneous BiCI in difficult everyday listening situations in which speech and noise come from different directions. Furthermore, bilaterally implanted patients were able to localize sounds with a precision, which was almost impossible for unilaterally implanted patients. In the current study, we focus on the results of this RCT 2 years after implantation. By using a between-subjects design, we present data concerning differences between UCI and BiCI. A within-subject design is used to compare the 1-year with the 2-year follow-up results of all patients. This procedure is used to prove

that the initial reported benefits of BiCI at 1-year follow-up remain stable over time.

MATERIALS AND METHODS

Study design and participants

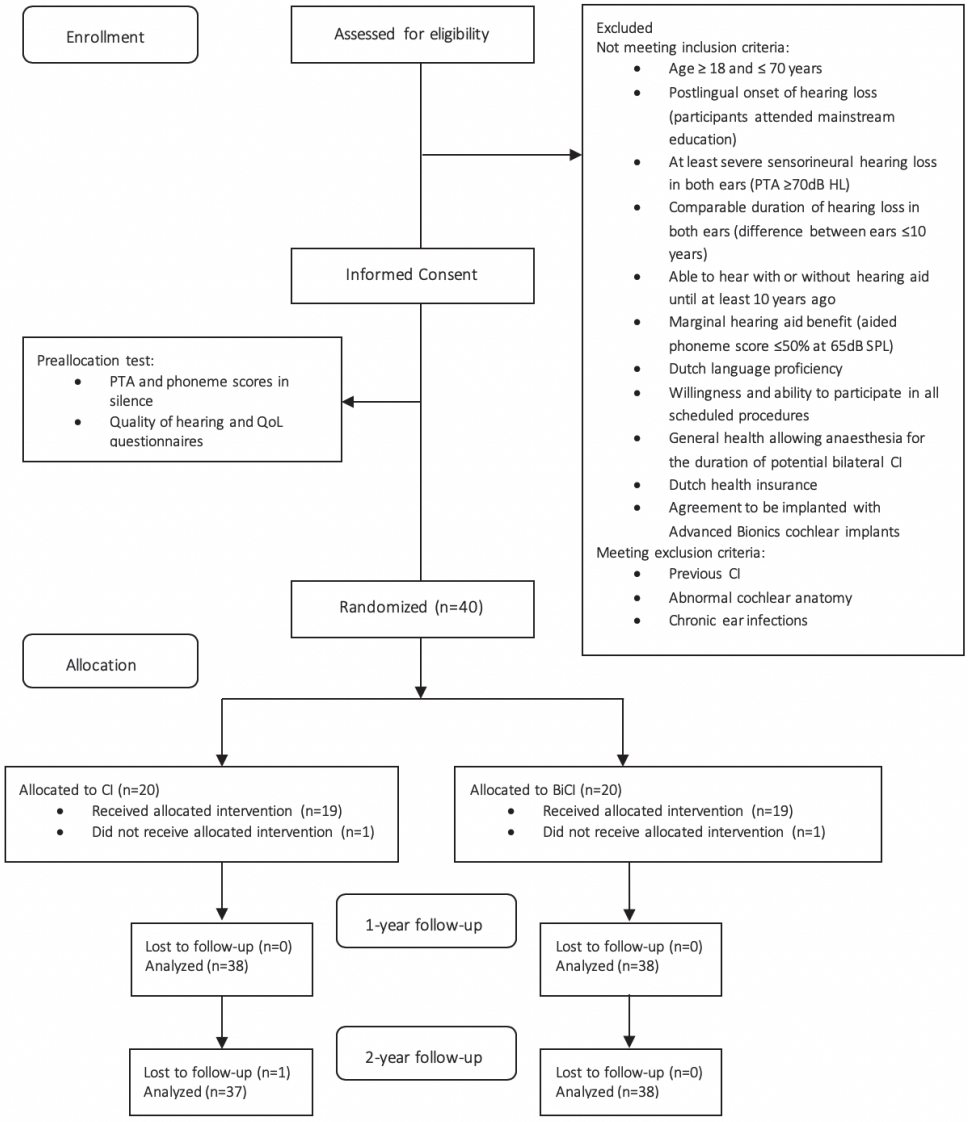
We conducted a multicenter RCT evaluating the benefits of simultaneous BiCI compared with UCI in adults with severe bilateral postlingual SNHL. We report data according to the descriptions of the Consolidated Standards of Reporting Trials (CONSORT) statement. The CONSORT statement comprises a 25-item checklist and a flow diagram. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.[14] More detailed information about the study design of this RCT is presented in the article we published earlier this year.[12]

This trial is designed and coordinated by the University Medical Center (UMC) Utrecht in collaboration with UMC Groningen, Leiden UMC, Maastricht UMC and Radboud UMC. The study was approved by the Human Ethics Committees of all participating centres (NL2466001808), registered in the Dutch Trial Register (NTR1722) and conducted according to the principles expressed in the Declaration of Helsinki.

Between January 2010 and September 2012, we discussed all patients eligible for CI in the five collaborating centres and verified in- and exclusion criteria for each patient. Baseline hearing tests were performed as part of the standard cochlear implant work-up and were equal in all centers. After receiving informed consent and self-reported questionnaires on hearing and quality of life (QoL), patients were randomly allocated to either 1) UCI or 2) simultaneous BiCI (Figure 1).

All patients were implanted with Advanced Bionics HiRes90K® implants. Implantation and rehabilitation were performed in patients' own hospital and rehabilitation started about six weeks after implantation. At hearing assessments patients used Harmony speech processors. We asked patients to complete the quality of hearing and QoL questionnaires again after one and two years of follow-up. Further hearing tests were performed at the UMC Utrecht by six well-trained researchers who strictly followed the same protocol.

Figure 1. Flowchart of enrollment



Abbreviations: BiCI, bilateral cochlear implantation; CI, cochlear implantation; PTA, pure-tone audiometry (average at 0.5, 1 and 2 kHz); SPL, sound pressure level; UCI, unilateral cochlear implantation; QoL, Quality of life.

The Dutch AB-York crescent of sound

Speech intelligibility in noise and sound localization capabilities were tested with the Dutch AB-York crescent of sound.[15] The test battery included: 1) the Utrecht - Sentence Test with Adaptive Randomized Roving levels (U-STARR),[16] 2) a speech intelligibility test with spatially separated sources (SISSS) and 3) a sound localization test. The spoken test language in the U-STARR and SISSS is Dutch. The scores of the U-STARR and SISSS are presented in decibels (dB); the lower the scores in dB, the better the hearing results. In the sounds localization test we presented the correct answers in percentages. The Smulders et al.[12] show more information about the test procedures and the AB-York crescent of sound.

All patients were tested in different listening conditions: 1) monaurally, with either one of the cochlear implants or the hearing aid switched on; 2) binaurally, using both cochlear implants; and 3) bimodally, with both cochlear implant and hearing aid switched on (when using a contralateral hearing aid).

To compare simultaneous BiCI with the next best option, we defined a patient's preferred situation for each patient in the unilateral group. This was their daily hearing situation; either wearing the cochlear implant only or a cochlear implant and hearing aid. Results from the bilateral group were compared with results of the patient's preferred situation from the unilateral group.

When sounds come from different directions, patients usually have a best performance situation and a worst performance situation. In general, a patient's best performance situation occurs when speech is presented to the ear with the best speech intelligibility in noise, and noise to the ear with the worst speech intelligibility in noise. In our study, speech intelligibility in noise is measured with the AB-York crescent of sound test setup. Sentences and noise coming from straight ahead at roving levels (65, 70, and 75dB). The noise was constantly adapted, dependent on the patient's performance, to find a critical SNR at which 50% of sentences were understood correctly. This level is called the Speech Reception Threshold in noise (SRTn). The lower the SRTn, the louder the noise compared to the sound, and the more challenging the test becomes for the listener.

In the unilateral group, speech presented to the cochlear implant side was always the best performing situation. In the bilateral group, the ear with the best SRTn was the best performing cochlear implant's side. In patients' worst performance situation, speech and noise come from the opposite sides as mentioned above.

Primary and secondary outcomes

Our outcomes were divided in objective and subjective outcomes.

The primary objective outcome measure was speech intelligibility in noise (SRTn), with speech and noise coming from straight ahead, measured with the U-STARR.[16]

Objective secondary outcomes were: 1) Speech intelligibility in noise with spatially separated sources (SISSS), 2) speech intelligibility in silence, measured with the standard Dutch phoneme test (using consonant-nucleus-consonant [CNC] words), and 3) localization capabilities.

Subjective secondary outcomes were self-reported benefits assessed with different quality of hearing and QoL questionnaires:

1. Speech, Spatial and Qualities Hearing Scale (SSQ). This questionnaire consists of three chapters of questions, namely speech (SSQ1), spatial hearing (SSQ2) and quality of hearing (SSQ3) in which patients were asked to rate their hearing capabilities on a 0-10 scale. A higher score indicates improvement on hearing. [17]
2. Time trade-off (TTO). We asked patients how many life years they were willing to give up to live the rest of their lives with perfect hearing. TTO (%) = ([Life expectancy - amount of years to give up for perfect hearing] / Life expectancy) X 100.[18]
3. Visual Analogue Scale (VAS). The VAS generally contains a thermometer with a scale from 0 to 100. Participants were asked to mark their general QoL from 0 (really bad) to 100 (perfect). These scores were then converted to values between 0 and 1, divided by 100.
4. Nijmegen Cochlear Implant Questionnaire (NCIQ). The NCIQ assesses six subdomains of hearing capabilities that are rated categorically (0-5 and "not applicable"). The questionnaires were analyzed using a well-described manual.[19]

5. The Ontario Health Utilities Index 3 (HUI3). The HUI3 is a measure of general health status. It contains questions on eight domains: vision, hearing, speech, ambulation, dexterity, cognition, emotion and pain. An overall multi-attribute utility score between 0.36 and 1 was analyzed according to the HUI3 manual.
6. The Dutch EuroQol-5D (EQ-D5). The Dutch EQ-D5 is a measure of general health status. It contains a VAS scale to rate QoL and five questions on mobility, self-care, daily activities, pain/complaints and anxiety/depression. To produce a single index value (ranging from 0.33-100) for health status, we analyzed these questions by using the descriptions of the EQ-D5 manual.[20,21]

Sample size calculation

To detect a clinically relevant difference of 3dB in SNR between groups on the hearing in noise test and a standard deviation of 3dB, with an α of 0.05 and a power of 80%, we calculated that fourteen subjects per group were needed. Three decibels is the generally adopted clinically relevant difference. To compensate for any potential loss to follow-up, five additional subjects were included in each group.

Statistical analysis

In order to compare baseline characteristics, we used the student's *t* test for numeric, normally distributed data and the χ^2 test for ordinal data.

Before analysis, all gathered data were double-checked by two independent persons who did not have any further connections to the otorhinolaryngology department. None of the results were normally distributed. Therefore, we applied nonparametric testing on statistically significant changes, and we calculated medians for all outcomes. For comparing the unilateral with the bilateral group we used the Mann-Whitney U test for all outcomes. The Wilcoxon signed ranked test was used to compare the 1-year follow-up data with the 2-year follow-up data.

RESULTS

Patient characteristics

The baseline characteristics of the 38 included patients are reported in Table 1. Four patients in the bilateral group did not use hearing aids before implantation. There were no other clinically significant differences in baseline characteristics. Hearing capabilities were similar in both treatment groups with average pure-tone audiometry thresholds of 106dB in the right ear and 108dB in the left ear.

Enrollment and completeness of data

Thirty-eight patients were randomly allocated to either 1) UCI or 2) simultaneous BiCI (Figure 1). After obtaining informed consent, two patients, one in each group, decided to withdraw prior to surgery. One patient, who was assigned to BiCI, was excluded when diagnosed with multiple myeloma only a few weeks later. Another patient, who was assigned to UCI, preferred to be implanted with another cochlear implant brand. Both patients were replaced by new patients. All other 38 patients completed the 1-year follow-up duration.

During the second follow-up year, one patient, who was assigned to UCI, decided to withdraw from the study for personal reasons. All second-year follow-up outcomes for this patient are missing, and therefore analyses were performed with the results of 37 patients.

The hearing tests were performed before implantation and after 1 and 2 years of follow-up. In the UCI group, 12 out of 19 patients used a contralateral hearing aid (bimodal hearing) at the 1-year follow-up test and 13 out of 18 after 2 years. The hearing tests were performed before implantation and after 1 and 2 years of follow-up. In the UCI group, 12 out of 19 patients used a contralateral hearing aid (bimodal hearing) at the 1-year follow-up test and 13 out of 18 after 2 years. Patients were tested in the same conditions as they are used to in normal life (average wearing duration 15.4 hours ± 1.5 standard deviation). For the speech-to-noise ratios used, the cutoff score was 130 dB, because then speech is presented in close to normal quiet conditions. Due to poor hearing performance, this occurred in one patient, who was assigned to UCI, on both the U-STARR and SISSS in both hearing conditions after 1 year of follow-up. After 2 years of follow-up, a cutoff score of 30 dB was used for the same patient in the worst performance situation on the SISSS; this was also done for another patient who was assigned to BiCI.

Table 1. Patient characteristics

Characteristics	UCI (n=19)	BiCI (n=19)
Gender, male:female	11:8	8:11
Age in years at CI	52.5 (12.5) [26-67]	47.8 (15.9) [18-70]
Age in years at onset of severe hearing loss		
Right ear	30.5 (20.1) [3-55]	30.5 (17.2) [3-63]
Left ear	30.6 (19.8) [3-55]	30.0 (17.5) [3-63]
PTA (dB)		
Right ear	106 (12) [78-125]	106 (16) [80-130]
Left ear	108 (13) [83-127]	108 (18) [77-130]
Maximum phoneme score (%)	46.2 (20.4) [0-80]	42.1 (27.6) [0-90]
Treatment hospital		
Utrecht	11	8
Maastricht	4	5
Nijmegen	2	3
Leiden	1	2
Groningen	1	1
Hearing aid use before CI		
Yes	19	15
No	0	4
Cause of deafness		
Hereditary	7	9
Unknown and progressive	9	6
Sudden Deafness	0	2
Head trauma	0	1
Meningitis	2	0
Rhesus antagonism	1	0
Sound exposure	0	1

Data are presented as mean (standard deviation) [range].
Abbreviations: BiCI, bilateral cochlear implantation; CI, cochlear implantation; PTA, pure-tone audiometry (average at 0.5, 1, and 2kHz); UCI, unilateral cochlear implantation.

UCI versus BiCI

Objective results

After a follow-up period of 2 years, we found no significant differences between UCI and simultaneous BiCI for our primary outcome (U-STARR),in which speech and noise were presented from straight ahead. In the UCI group, the median SRTn was 9.8 dB (range, 1.6 to 22.5), compared to 7.5 dB (range, 0.6 to 19.4) in the BiCI group (Table 2).

The median phoneme score in silence, measured with single CNC words presented from straight ahead, was also similar in both groups. The CNC score was 88.5% (range, 52.0% to 98.0%) in the UCI group, compared to 88.0% (range, 55.0% to 100.0%) in the BiCI group.

In this study, BiCI proved the most beneficial when speech and noise come from different directions and speech was presented to the worst ear (the nonimplanted ear in the UCI group and the ear with the worst performing condition in the BiCI group). The median SRTn score was 13.3 dB (range, 5.3 to 30.0) in the UCI group, versus 5.9 dB (range, 24.7 to 30.0) in the BiCI group (P = 0.01). No significant differences between groups were reported on the SISSS if speech was presented to the ear with the best SRTn and noise to the ear with the worst SRTn (best performance situation). The median SRTn score was 3.8 dB (range, 23.8 to 30.0] in the UCI group and 2.5 dB (29.1 to 13.1) in the BiCI group.

Patients in the BiCI group performed significantly better on sound localization in all possible test conditions. When sounds were presented from 15°, median correct localization scores were 23.3% (range, 13.3% to 46.7%) in the UCI group and 53.3% (range, 16.7% to 90.0%) in the BiCI group ($P < 0.01$). When presented from 30°, these scores were 26.7% (range, 6.7% to 56.7%) in the UCI group and 63.3% (range, 36.7% to 100.0%) in the BiCI group ($P < 0.01$), and when presented from 60°, the scores were 46.7% (range, 30.0% to 90.0%) and 96.7% (range, 66.7% to 100.0%), respectively ($P < 0.01$).

Table 2. Objective outcomes after 2 years of follow-up: unilateral versus bilateral cochlear implantation

	UCI (n=18)	BiCI (n=19)	*P* value*
Speech in noise from straight ahead (SRTn in dB)	9.8 (1.6-22.5)	7.5 (0.6-19.4)	NS
Phoneme score in silence (CNC in %)	88.5 (52.0-98.0)	88.0 (55.0-100.0)	NS
Speech and noise from different directions (SRTn in dB)			
SISSS best performance situation	3.8 (-3.8-30.0)	2.5 (-9.1-13.1)	NS
SISSS worst performance situation	13.3 (5.3-30.0)	5.9 (-4.7-30.0)	0.01**
Localization of sounds			
60° (% correct)	46.7 (30.0-90.0)	96.7 (66.7-100.0)	<0.01**
30° (% correct)	26.7 (6.7-56.7)	63.3 (36.7-100.0)	<0.01**
15° (% correct)	23.3 (13.3-46.7)	53.3 (16.7-90.0)	<0.01**

Data are presented as median (range).
** Mann-Whitney U test.*
*** Significant (P < 0.05).*
Abbreviations: BiCI, bilateral cochlear implantation; CNC, consonant-nucleus-consonant words; NS, not significant (P > 0.05); SISSS, speech in spatially separated sources; SRTn, speech reception threshold in noise; UCI, unilateral cochlear implantation.

Subjective results

At the 2-year follow-up, patients in de BiCI group reported significantly better results on speech intelligibility in silence, background noise, resonating environments, and on the telephone (SSQ1) and on quality of hearing (SSQ2); median SSQ1 scores were 5.9 (range, 2.2 to 8.8) in the BiCI group versus 3.1 (range, 1.7 to 8.3) in the UCI group ($P = 0.01$), and median SSQ2 scores were 6.6 (range, 2.9 to 8.1) and 2.4 (range, 5.0 to 7.3), respectively ($P < 0.01$) (Table 3). Bilaterally implanted patients also reported better results on spatial hearing (SSQ1), but these benefits were not significant ($P < 0.05$). On the VAS on hearing and the NCIQ, the BiCI group reported better hearing capabilities, although they did not differ significantly from the UCI group. We did not find a significant difference between groups on the QoL questionnaire results (i.e., TTO, EQ-5D, HUI3).

Table 3. Subjective outcomes after 2 years of follow-up: unilateral versus bilateral cochlear implantation

	UCI (n=18)	BiCI (n=19)	*P* value*
VAS			
Health	80.0 (65.0-100.0)	80.0 (55.0-95.0)	NS
Hearing	65.5 (0.0-94.0)	75.0 (40.0-90.0)	NS
TTO	100.0 (50.0-100.0)	100.0 (85.0-100.0)	NS
SSQ			
SSQ 1	3.1(1.7-8.3)	5.9 (2.2-8.8)	0.01**
SSQ 2	2.4 (5.0-7.3)	6.6 (2.9-8.1)	<0.01**
SSQ 3	4.4 (3.6-10.3)	6.1 (3.7-8.5)	NS
EQ-D5			
Total utility score	1.0 (0.8-1.0)	1.0 (0.7-1.0)	NS
Thermometer	85.0 (62.0-100.0)	77.0 (50.0-100.0)	NS
HUI3			
Multi-attribute utility score	0.7 (0.4-0.9)	0.8 (0.5-0.9)	NS
NCIQ			
Basic sound perception	88.7 (32.5 -100.0)	90.0 (60.0-100.0)	NS
Advanced sound perception	88.7 (32.5-97.5)	91.7 (60.0-100.0)	NS
Speech production	46.5 (17.7-85.0)	62.5 (35.0-95.0)	NS
Self esteem	62.5 (25.0-92.5)	75.0 (57.2-92.5)	NS
Activity	70.0 (25.0-97.5)	77.5 (43.8-95.0)	NS
Social interactions	62.5 (27.5-77.8)	63.9 (38.9-88.9)	NS

Data are presented as median (range).
** Mann-Whitney U test.*
*** Significant (P < 0.05).*
Abbreviations: BiCI, bilateral cochlear implantation; EQ-D5, EuroQol-5D; HUI3, Health Utility Index; NCIQ, Nijmegen cochlear implant questionnaire; NS, not significant (P > 0.05); SSQ, speech, spatial and qualities hearing scale; TTO, time trade-off; UCI, unilateral cochlear implantation; VAS, visual analogue scale.

1-year follow-up versus 2-year follow-up

When we compared the 1-year follow-up data with the 2-year follow-up data, no significant differences were found for any of the objective and subjective outcomes (Table 4 and Table 5).

Table 4. Objective outcomes: 1-year versus 2-year follow-up for all patients

	1-year FU (n=38)	**2-year FU (n=37)**	***P* value***
Speech in noise from straight ahead (SRTn in dB)	8.4 (0.3-30.0)	8.1 (0.6-22.5)	NS
Phoneme score in silence (CNC in %)	85.0 (67.0-100.0)	88.0 (52.0-100)	NS
Speech and noise from different directions (SRTn in dB)			
SISSS best performance situation	5.0 (-4.7-30.0)	3.4 (-9.1-30.0)	NS
SISSS worst performance situation	11.3 (-2.8-30.0)	10.0 (-4.7-30.0)	NS
Localization of sounds			
60° (% correct)	83.3 (30.0-100.0)	76.7 (30.0-100.0)	NS
30° (% correct)	50.0 (16.7-96.7)	46.7 (6.67-100)	NS
15° (% correct)	36.7 (20.0-90.0)	36.7 (13.3-90.0)	NS

Data are presented as median (range).

** Wilcoxon signed rank test.*

Abbreviations: CNC, consonant-nucleus-consonant words; FU, follow-up; NS, not significant (P > 0.05); SISSS, speech in spatially separated sources; SRTn, speech reception threshold in noise.

Table 5. Subjective outcomes: 1-year versus 2-year follow-up in all patients

	1-year FU (n=38)	2-year FU (n=37)	*P* value*
VAS			
Health	80.0 (45.0-99.0)	80.0 (55.0-100.0)	NS
Hearing	70.0 (20.0-90.0)	70.0 (0.0-94.0)	NS
TTO	100.0 (85.0-100.0)	100.00 (85.0-100.0)	NS
SSQ			
SSQ 1	4.8 (1.1-8.6)	4.9 (1.7-8.8)	NS
SSQ 2	4.8 (1.2-8.0)	5.2 (5.0-8.2)	NS
SSQ 3	5.9 (4.4-9.5)	5.6 (3.6-10.3)	NS
EQ-D5			
Total utility score	1.0 (0.3-1.0)	1.0 (0.7-1.0)	NS
Thermometer	77.5 (45.0-100.0)	80.0 (50.0-100.0)	NS
HUI3			
Multi-attribute utility score	0.8 (0.4-0.9)	0.8 (0.3-0.9)	NS
NCIQ			
Basic sound perception	92.5 (32.5-100.0)	90.0 (32.5-100.0)	NS
Advanced sound perception	92.5 (32.5-100.0)	90.0 (32.5-100.0)	NS
Speech production	58.6 (22.5-90.0)	57.5 (17.5-95.0)	NS
Self esteem	73.8 (22.2-94.4)	72.5 (25.0-92.5)	NS
Activity	75.0)25.0-97.5)	75.0 (25.0-97.5)	NS
Social interactions	63.9 (25.0-88.9)	63.9 (27.5-88.9)	NS

Data are presented as median (range).

** Wilcoxon signed rank test.*

EQ-D5, EuroQol-5D; FU, follow-up; HUI3, Health Utility Index; NCIQ, Nijmegen cochlear implant questionnaire; NS, not significant (P > 0.05); SSQ, speech, spatial and qualities hearing scale; TTO, time trade-off; VAS, visual analogue scale.

DISCUSSION

In this study, we presented the results after 2 years of follow-up of the first RCT investigating the benefits of simultaneous BiCI compared with UCI in postlingually deafened adults. Earlier, our study group published the results after one year of follow-up.[12] The major strength of our study is that allocation bias is minimized by performing an RCT. In most studies concerning UCI versus BiCI, bilateral implantees were asked to turn off one cochlear implant to assess differences between monaural and binaural hearing. [1,9] Since these patients

were trained to listen with two implants in daily life, and because insertion of a cochlear implant might have damaged the cochlea, this is not representative for actual unilateral implantation. In our study, the contralateral cochlea was untreated in the unilateral group. This way, UCI versus BiCI can be studied appropriately.

We showed that simultaneous BiCI is effective in restoring spatial hearing performances after a 1-year follow-up. A significant benefit of BiCI was found on the SISSS in the worst performance situation and for sound localization in all possible test conditions. These findings were confirmed by questionnaires concerning hearing; bilateral implanted patients scored significantly better on the VAS on hearing and on all three domains of the SSQ. We found comparable results for the UCI and BiCI group when speech and noise both came from straight ahead, and for the phoneme score in silence.

In this study, we report objective significant benefits of BiCI after 2 years of follow-up. Based on the subjective test results, bilaterally implanted patients only showed a significant benefit on the SSQ1 concerning speech and the SSQ2 concerning spatial hearing. Better hearing capabilities were also reported on the SSQ3 concerning quality of hearing and on the VAS on hearing, but these differences were not significant (P = 0.05 and 0.06 respectively). Because bilaterally implanted patients gained similar benefits after 2 years of follow-up when compared to 1 year of follow-up, we conclude that simultaneous BiCI leads to a long-term benefit.

The within-subject design of this study allowed us to observe that there are no significant changes of the outcome measures following the first year. We showed no significant benefit from the second year of implant use.

Therefore, in future studies regarding CI, a follow-up duration of 1 year may be considered as a reliable evaluation period when looking at speech in noise and spatial hearing. Most studies published on the potential benefits of UCI versus BiCI reported results measured after a follow-up period of less than 1 year or did not report their duration of follow-up at all.[9] Only two studies provided a follow-up of 1 year. [22,23]

Significant hearing benefits of BiCI compared to UCI were reported here after a follow-up period of 2 years. These benefits were not confirmed with any of the general QoL questionnaires we used. This can be explained by the fact that CI, either unilateral or bilateral, will provide important benefits in daily life when compared to the preoperative situation. The potential additional benefit of a second cochlear implant concerning QoL can only be investigated properly by using a within-subject design, in which unilaterally implanted patients will receive a second implant.

In the current study, we compared simultaneous BiCI with UCI or bimodal hearing, to represent the real-life situation as much as possible. Even in this study set-up, bilaterally implanted patients performed better in difficult listening situations.

CONCLUSION

This study demonstrates that bilaterally implanted adult patients benefit significantly from their second cochlear implant, when compared with unilaterally implanted patients in everyday listening situations in which speech and noise come from different directions. Also, bilaterally implanted patients are able to localize sounds with a high degree of certainty, whereas unilaterally implanted patients cannot. The benefits patients in the bilateral group derive from a second cochlear implant are stable over the second year of implant use. We may conclude that simultaneous BiCI offers long-term benefits in adults with severe bilateral postlingual SNHL.

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CHAPTER

4

Development of a squelch effect in adult patients after simultaneous bilateral cochlear implantation

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ABSTRACT

Objectives

To investigate whether a squelch effect occurs in the first 3 years following simultaneous bilateral cochlear implantation (BiCI) and to investigate whether this effect increases during follow-up.

Study design and patients

Prospective study as part of a multicenter randomized controlled trial (RCT) on the benefits of BiCI over unilateral cochlear implantation (UCI). In nineteen postlingually deafened adults.

Intervention

Simultaneous BiCI.

Main outcome measure

The squelch effect, measured yearly with a speech intelligibility in noise test with spatially separated sources. Bilateral results were compared to unilateral results in which the cochlear implant at the noise side was turned off. The squelch effect was investigated for the patients' best performing ear and for the left and right ear separately.

Results

In 13 individual patients, a squelch effect was present after 1 year. This number increased during follow-up years. On group level, a squelch effect was present in patients' best performing ear after two and 3 years (1.9 dB). A squelch effect was present in both ears after 3 years (AS: 1.7 dB, AD: 1.3 dB).

Conclusion

Patients who underwent simultaneous BiCI developed a measurable benefit from the squelch effect after 2 years in their best performing ear and after 3 years in both ears. These observations suggest that the brain learns to use interaural differences to segregate sound from noise after simultaneous bilateral BiCI. The squelch effect increased over time which suggests a growth in cortical integration and differentiation of inputs from bilateral cochlear implants due to brain plasticity.

INTRODUCTION

Cochlear implantation (CI) has become a widely accepted treatment for patients with severe to profound hearing loss who obtain limited benefit from conventional hearing aids. Although many patients with a single cochlear implant achieve relatively high levels of speech perception in silence, even the most successful implantees have difficulties with speech perception in noise. These difficulties may be overcome in bilaterally implanted patients by the availability of binaural hearing due to sound input in both ears.[1–4]

Hearing with two ears, binaural hearing, is based on three principles: 1) The head shadow effect occurs in spatially separated speech and competing noise. The presence of the head results in differentiated signal to noise ratios (SNRs) between both ears due to differential filtering of sounds (high vs low frequency). With two functional ears the subject is able to attend to the ear with the most favorable SNR. 2) The binaural summation effect occurs when speech and noise originate from the same location. Binaural summation is the ability of the auditory system to combine input from both ears and to derive benefit from this combined information centrally. Binaural summation leads to increased perceived loudness of sounds. 3) The squelch effect occurs in spatially separated speech and competing noise situations. Squelch is the ability of the auditory system to combine the information from both ears centrally and segregate the speech from the noise by the differences in sound between both ears. Specifically, the brain is able to suppress the noise by utilizing this noise information coming from the ear with the poorer SNR. Through this segregation, a subject's speech perception in noise is improved.[5]

In literature there is evidence suggesting that when listening with both ears, normal hearing listeners are able to receive a 3 to 5dB binaural squelch.[6–8] In normal and impaired hearing the psychophysical phenomena related to the squelch effect are termed binaural masking level difference[9], comodulation masking release[10], in the order of 1.3 dB for speech, and spatial release from masking[11], in the order of 5.1dB for the best-aided bilateral condition. The terms refer to various implementations of test paradigms in which the perception in one ear, of a tone or speech presented in an interfering sound, is improved by presenting the interfering sound also to the other ear. The improvement is due to central auditory processing mechanisms, working on top of the other effects, summation and head shadow, known for improving binaural perception.

Binaural hearing is superior to monaural hearing in normal hearing listeners and bilateral hearing aid users, which resulted in bilateral hearing aid fitting as standard care two decades ago.[1,12,13] For bimodal cochlear implant users (e.g., combination of a cochlear implant and hearing aid) the additional benefit of a hearing aid is limited in patients with little to no residual hearing.[14–16] In a study with 35 bimodal patients with a CNC hearing aid score of 12.4 dB (13.9) no squelch effect was seen (-0.7 dB) in the cochlear implant ear.[11] Since speech perception is limited through the hearing aid ear, there is poor auditory information input to the brain from this ear, hampering a squelch effect in bimodal patients.

The squelch effect has also been investigated in bilateral cochlear implant users.[5,17–26] Most studies were retrospective cohort studies or cross-sectional studies with small sample sizes and study populations comprised of simultaneously and sequentially implanted patients. Most of these studies showed benefits of the head shadow and binaural summation effects, but limited evidence for the squelch effect. Two studies reported a lack of squelch effect after a follow-up period of 6 months.[21,26] In another study, a squelch effect was seen in 3 out of 10 simultaneously implanted patients after 1 year of follow-up.[17] Another study found a squelch effect in the left ear in a group of sequentially implanted patients, at least 1 month after the second implantation, but not in the right ear.[22] Six months after implantation, a squelch effect was objectified in 50% of 34 sequentially implanted patients.[24] In a study with 25 simultaneously and 1 sequential bilaterally implanted patients using fixed SNRs, a significant squelch effect was seen in the whole group after 1 year follow-up, which was not yet present after 6 months.[27] In a longitudinal study of nine simultaneously bilaterally implanted patients, an increase in the squelch effect was seen over a 4 year period.[28]

In literature generally two test set-ups are used. First, a set-up with speech from straight ahead (0° azimuth) and noise from the side (+90° azimuth and -90° azimuth). Second, a set-up with speech from one side (45 or 60° azimuth) and noise from the other side (-45° or -60 azimuth).[21,26] The second is less sensitive to estimate the head shadow effect but more sensitive to detect the binaural squelch effect.[2] The squelch effect can be measured in various ways. First, it is measured at a fixed SNR of 10dB, then the squelch effect is expressed as an increase in percentage correct scores at 10dB SNR. Second, it can be expressed as the gain in the SRTn, that is the SNR at which patients score 50% of sentences correctly.[22]

In our prospective study, we investigated the presence of the squelch effect in 19 simultaneously bilaterally implanted cochlear implant users after a follow-up of 3 years. The aim of this study is twofold: to evaluate if there is an apparent squelch effect in simultaneously bilaterally implanted patients and to evaluate if there is an increase in the squelch effect due to what we would normally call cochlear implant users' learning curve but is in fact central adaptation due to brain plasticity.[29]

MATERIAL AND METHODS

Study design and participants

The current study was embedded in a multicenter randomized controlled trial (RCT) on the benefits of simultaneous over sequential bilateral cochlear implantation (BiCI) in adults with severe bilateral post lingual sensorineural hearing loss (SNHL).[4] The University Medical Center (UMC) Utrecht designed and coordinated this RCT. Inclusion and treatment of patients was done in collaboration with Maastricht UMC, Radboud UMC, Leiden UMC and UMC Groningen.

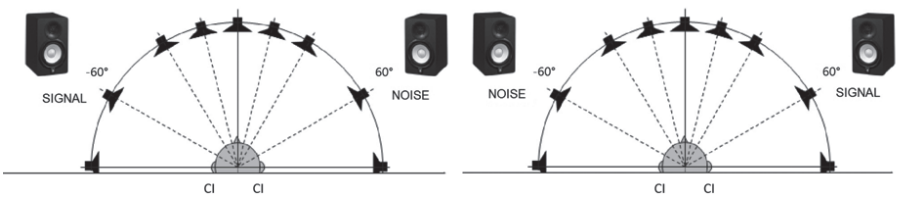
Thirty-eight patients were randomized to either 1) sequential BiCI or 2) simultaneous BiCI. All patients were implanted with Advanced Bionics HiRes90K® CIs and used Harmony speech processors. For more detailed information concerning the study protocol of this RCT we refer to the previous article of our study group.[4] In this study we evaluated the squelch effect in the 19 simultaneously bilaterally implanted patients during a 3-year follow-up period. Data were reported according to the CONSORT statement. The study was approved by the Human Medical Ethics Committees of all participating centers (NL2466001808), registered in the Dutch Trial Register (NTR1722) and conducted according to the principles expressed in the Declaration of Helsinki.

Test set-up

The speech intelligibility in noise with spatially separated sources (SISSS) test was conducted using the AB-York crescent of sound test set-up, which included the Utrecht - Sentence Test with Adaptive Randomized Roving levels (U-STARR).[30]

Sentences were presented from 60° to the left (-60° azimuth) or right (+60° azimuth) of the subject and speech-spectrum-shaped noise was presented from 60° at the opposite side (See Figure 1). We chose this set-up since this is a more realistic representation of the everyday listening situations in noise, in which a subject will turn his head with his best ear towards the signal and his worst ear towards the noise and since this set-up is more sensitive to detect a squelch effect. A sentence was scored as correct when a subject repeated at least 3 out of 5 or 2 out of 3 keywords correctly. Sentences were roving at 65, 70 or 75dB sound pressure level (SPL) with an initial signal to noise ratio (SNR) of +20dB. When a sentence was scored as correct, the SNR of the next sentence was reduced. If a sentence was scored as incorrect, the SNR of the next sentence was increased. In the first phase, the SNR was reduced or increased in 10dB steps following a correct or incorrect response. In phase two and three, steps of 5 and 2.5dB were used. Progression from phase 1 to 2 and phase 2 to 3 occurred whenever a reversal occurred, for example when 2 sentences scored correct were followed by an incorrect sentence. The average SNR of the last sixteen sentences, all in phase 3, was calculated, resulting in the speech reception threshold in noise (SRTn). A cut-off of 30dB was used, as this score or higher was considered a situation with virtually no noise. Patients could adjust the speech processor programs to their preference, therefore microphone settings may differ between patients. Since this was no variable of interest, no data concerning microphone settings was gathered. Loudness balancing was done prior in a clinical setting and patients were asked to balance volume between both cochlear implants.

Figure 1.



Measuring the squelch effect in the SISSS. The SISSS was performed with a) speech from the left and noise from the right (S-60N+60) and b) vice versa (S+60N-60) while using the left, right and both CIs. The best performing ear was determined by the best bilateral score with speech from the left (S-60N+60) or the right (S+60N-60).
Abbreviations: CI, cochlear implants; SISSS, speech intelligibility in noise with spatially separated sources.

Main outcome measure

The main outcome measure of this prospective study was the squelch effect. To calculate a squelch effect, the SISSS was evaluated in both the bilateral and unilateral condition (by turning the cochlear implant off at the side of the noise). By comparing these conditions, the additional effect of the second implant was calculated. The sequence of measurement was structurally equal: first the bilateral condition, then the unilateral conditions, starting with CI1 followed by CI2. The condition with speech from the left and noise from the right was tested first followed by the condition in which speech and noise were reversed.

When sounds come from different directions, patients usually have a best performing side. To establish a patient's best performing side, we determined the ear with the best score in the bilateral situation when speech came either from left or right. For example, if a patient's best SRTn was when speech came from the left and noise from the right, this patient's best performing side was left.[30]

Statistical analyses

Before analyzing the data, data were double-checked by two independent persons without connections to the Utrecht otorhinolaryngology department. None of the scores were normally distributed, thus we reported medians and interquartile ranges, except for variables containing the amount of the squelch effect, which were normally distributed. The squelch effect was derived from the data multiple times: for both ears separately and for the patient's best performing ear only. To compare the bilateral and unilateral results, the Wilcoxon signed rank test was used. To compare the outcomes between years of follow-up, the Friedman and Wilcoxon signed rank test were used. To compare the proportions of patients with a squelch effect during follow-up, a Fisher's Exact Test was used. We recalculated the proportions using a minimum difference of 1SD of the normal hearing people SISSS results to only include the patients that exhibit a clinically relevant squelch effect, which was 2.0dB for S+60 N-60; 1.7 dB for S-60 N+60 and 1.8 dB for the best performing ear.[30] Data were presented including and excluding patient 19 from the 3 year follow-up data because of non-use of his right cochlear implant due to pain complaints. SPSS version 21.0.0 for Windows was used and a *P* value <.05 was considered statistically significant.

RESULTS

Participants were included between January 2010 and August 2012. The baseline characteristics of these patients are reported in Table 1. One patient was diagnosed with Kahler's disease a few weeks after inclusion and was therefore replaced by another patient. No patients were lost to follow-up during the 3-year follow-up. As mentioned above, due to pain at the right implant site, one patient did not wear his right CI for several months between the 2nd and 3rd year of follow-up. In the analyses, this patient's 3-year follow-up data are shown in the data and interpreted separately.

Left and right

Figure 2 depicts boxplots of the median SRTn in the bilateral and the unilateral conditions for the left and right ear separately. Median scores after 1 and 2 year did not differ between both conditions. After 3 years, a significant squelch effect for the left ear was seen. The median SRTn was 4.4dB [0.3 – 9.1] in the bilateral situation and 5.0dB [1.6 – 8.4] in the unilateral situation ($P = 0.038$). When looking at the data for the right ear, Figure 3 clearly shows that the bilateral SRTn of patient 19 clearly deteriorated due to non-use of his right CI over time. This score for sound from the right and noise from the left is an outlier in comparison to the other scores and this patient's prior scores. After exclusion of this patient from this analysis, a squelch effect on group level was present: bilateral median SRTn: 2.7dB [-1.7 – 7.6] and unilateral median SRTn: 4.3 [-0.9 – 6.9] ($P = 0.045$).

The proportion of patients that demonstrated a squelch effect in the left ear was 8/19 (42%) after 1 year, 8/19 (42%) after 2 years, and 13/18 (72%) after 3 years (excluding patient 19). When applying a minimum difference of 1.7 dB between both conditions, the proportions were 4/19 (21%) after 1 year, 8/19 (42%) after 2 years, and 9/18 (50%) after 3 years.

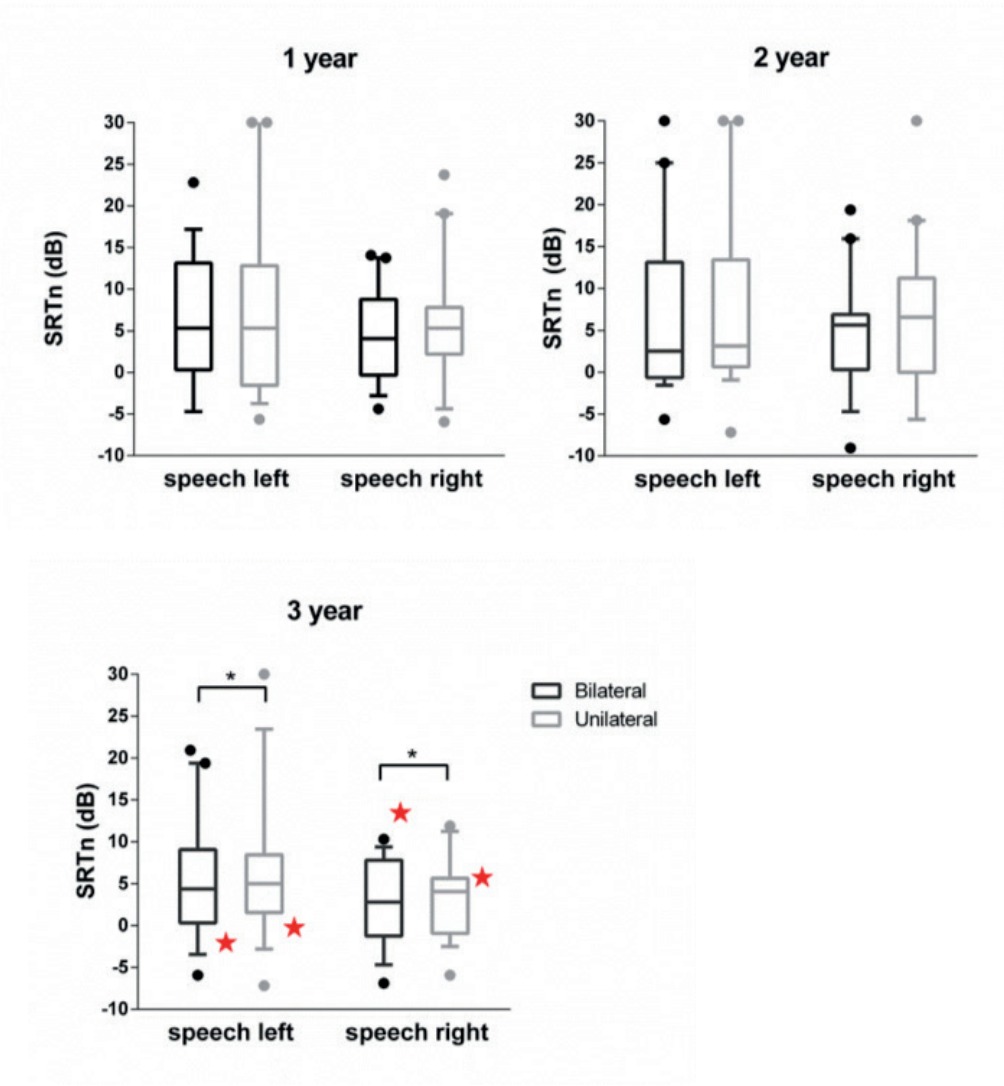
The proportion of patients that demonstrated a squelch effect in the right ear was 11/19 (58%) after 1 year, 14/19 (74%) after 2 years, and 13/18 (72%) after 3 years (excluding patient 19). When applying a minimum difference of 2.0 dB, the proportions were 9/19 (47%) after 1 year, 8/19 (42%) after 2 years, and 7/18 (39%) after 3 years.

Table 1. Patient characteristics

Characteristics	Simultaneous BiCI (n=19)
Gender, male:female	8:11
Age in years at CI	47.8 (15.9) [18-70]
Age in years at onset of severe hearing loss	
Right ear	30.5 (17.2) [3-63]
Left ear	30.0 (17.5) [3-63]
PTA (dB)	
Right ear	106 (16) [80-130]
Left ear	108 (18) [77-130]
Maximum phoneme score (%)	42.1 (27.6) [0-90]
Treatment hospital	
Utrecht	8
Maastricht	5
Nijmegen	3
Leiden	2
Groningen	1
Hearing aid use before CI	
Yes	15
No	4
Cause of deafness	
Hereditary	9
Unknown and progressive	6
Sudden Deafness	2
Head trauma	1
Meningitis	0
Rhesus antagonism	0
Sound exposure	1

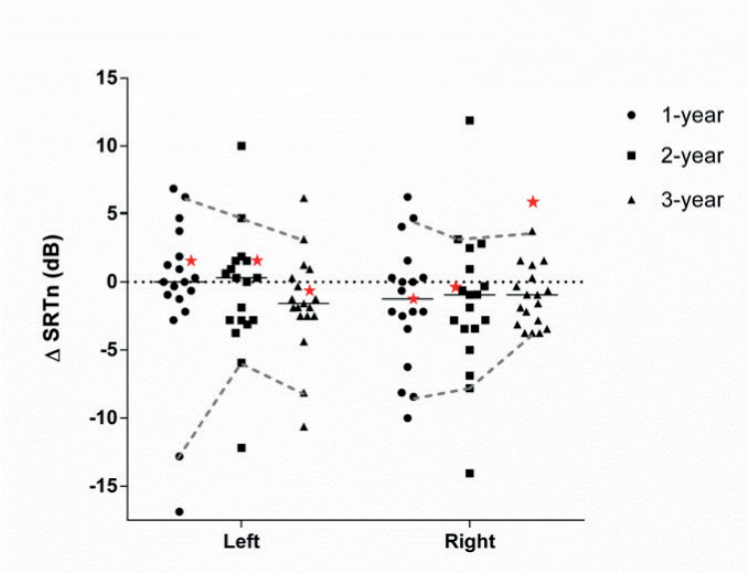
Data are presented as mean (standard deviation) [range].
Abbreviations: BiCI, bilateral cochlear implantation; CI, cochlear implantation; PTA, pure-tone audiometry (average at 0.5, 1, and 2kHz).

Figure 2.



*Boxplot of bilateral and unilateral scores in both ears during a 3-year follow-up. The red asterix indicates the scores of patient 19 who did not wear his right cochlear implant before the 3rd follow-up year. The worsening of the bilateral score when speech came from the right indicates the deterioration of right side hearing. Without this patient, a squelch effect was present for the left and right ear on group level. With this patient, however, this was not significant for the right ear anymore. The median is marked by the horizontal line in the boxes; the 25th and 75th percentiles are marked by the ends of the boxes; the 10th and 90th percentiles are marked by the whiskers; the outliers are displayed by the filled circles; * Wilcoxon signed rank test $p < 0.05$.*

Figure 3.



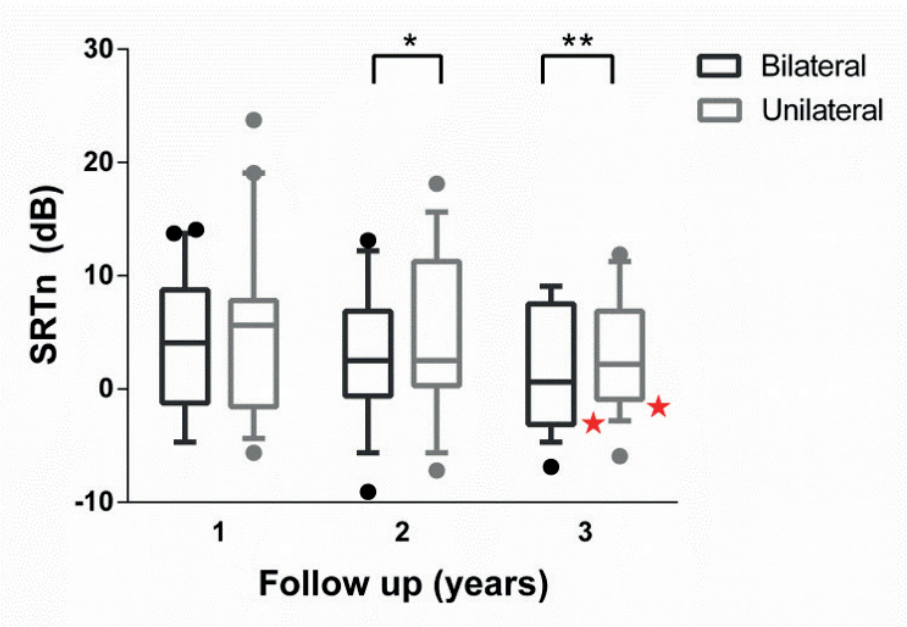
Squelch effect for the left (S-60 N+60) and right ear (S+60 N-60). The patients' difference (bilateral – unilateral scores) for the left and right ears during 3 years of follow-up. A score below zero portrays a squelch effect. The median value is indicated with the horizontal line. The 10th and 90th percentile are depicted with a grey dashed line. The red asterisks point out the scores of patient 19. This figure shows his deterioration of bilateral integration of sounds when speech comes from the right and noise from the left after 3 years of follow-up in this patient.

Best performing situation

Figure 4 shows boxplots of the median SRTn in the bilateral and the unilateral condition for our patient's best performing ear during a 3-year follow-up. After 1 year, no difference between both conditions was objectified. After 2 years, there was a significant difference (2.5 dB [-0.6 – 6.9] bilateral compared to 2.5 dB [0.3 – 11.3] unilateral $P = 0.035$). After 3 years, the squelch effect was larger with a bilateral SRTn of 0.6 dB [-3.1 – 7.5] compared to a unilateral SRTn of 2.2 dB [-0.9 – 6.9] (analysis with 19 patients, left ear of patient 19's best performing ear was his left ear, $P = 0.006$).

The proportion of patients who demonstrated a squelch effect in the best performing ear was 13/19 (68%) after 1 year, 12/19 (63%) after 2 years, and 16/19 (84%) after 3 years. After applying a minimum difference of 1.8 dB, the proportions were 8/19 (42%) after 1 year, 9/19 (47%) after 2 years, and 10/19 (53%) after 3 years.

Figure 4.

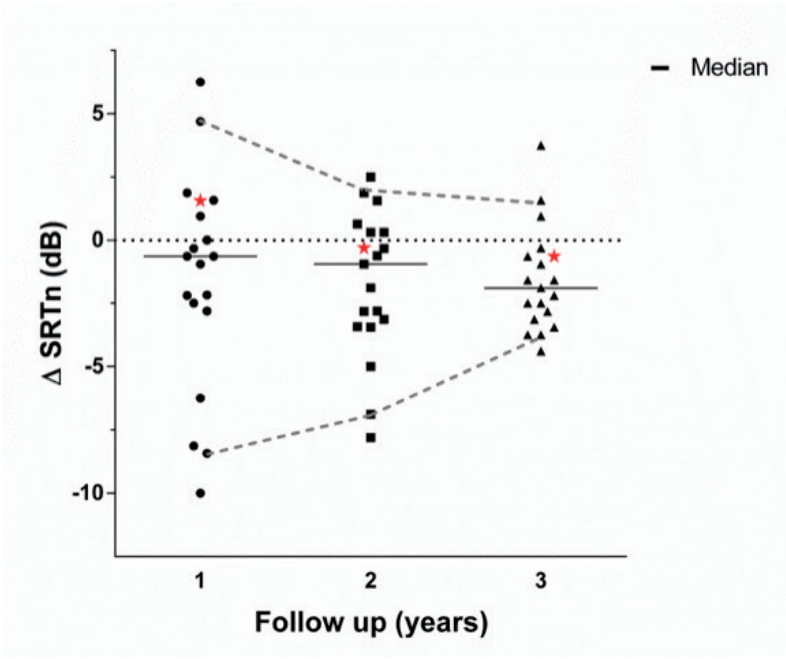


*Boxplot of squelch effect in the best performing ear during a 3-year follow-up. After 2 and 3 years, a squelch effect was present for patients' best performing ear. The red asterisks out the scores from the left ear of patient 19. The median is marked by the horizontal line in the boxes; the 25th and 75th percentiles are marked by the ends of the boxes; the 10th and 90th percentiles are marked by the whiskers; the outliers are displayed by the filled circles; * Wilcoxon signed rank test $p < 0.05$.*

Comparing follow-up years

As Figure 3, Figure 5 shows the absolute squelch effect: an advantage associated with bilateral listening as compared with the shadowed ear alone in case the signal and masker are presented from different locations in the horizontal plane. In this figure, the 10th and 90th percentile lines are depicted. What is striking, especially in Figure 5, is the narrowing of variation of scores as time progresses which results in the significance of the squelch effect on group level. This development indicates that patients exhibit a different development of their hearing abilities with two cochlear implants.

Figure 5.



Squelch effect for the best performing ear. The difference (bilateral – unilateral scores) for the best performing ear during 3 years of follow-up. A score below zero portrays a squelch effect. The median value is indicated with the horizontal line. The 10th and 90th percentile are depicted with a grey dashed line. The range of difference decreases evidently during follow-up. After 3 years, only 3 patients show a positive difference score. The red asterisks point out the score of patient 19.

DISCUSSION

Synopsis of study results

In this study we investigated the presence of a squelch effect in an RCT of simultaneous bilaterally implanted postlingually deafened adults during a 3-year follow-up. In 13 individual patients, a squelch effect was already present in at least one ear after one year. On group level, a squelch effect was present in a patient's best performing ear after 2 and 3 years. We found a squelch effect in the left and right ear after 3 years.

Comparison to the existing literature

In literature concerning the squelch effect in bilateral cochlear implant users, follow-up periods range from 6 months to 4 years.[24,28] Generally, a squelch effect on group level was seen in studies with at least 1 year of follow-up.[17,27,28] Six months after implantation, a squelch effect was generally not seen or only in individual patients[21,24,26] An increase of the squelch effect was seen in a study by Eapen et al. during a 4-year follow-up, indicating that the squelch effect advanced with greater listening experience.[28] In accordance to literature, in our study a squelch effect was seen in individual subjects after 1 year, but on group level only after 2 years and became more robust after 3 years. Van Hoesel stated that binaural unmasking benefits for bilateral CI patients are generally minimal.[16] Gifford et al. found a squelch effect for the 1st and 2nd implanted ear of 0.9dB and 2.3 dB in a group of 30 bilaterally implanted patients, of which four were implanted simultaneously.[11] Another study found a squelch effect size of 0-2 dB with a single interfering noise.[8] In our study, we found a squelch effect in the amount of 0.6 dB after 1 year (not significant), 0.9 dB (significant) and 1.9 dB after 3 years (significant) for the best performing ear. After 3 years, the squelch effect amounted to 1.7 dB in the left ear and 1.3 dB in the right ear. These numbers are in accordance to the previous studies on the binaural squelch effect. Our results suggest a development and increase of the squelch effect in the years following BiCI. This effect implies that the brain is able to integrate different cues of sound to segregate sound from noise.[28] Better separation of sound from noise improves hearing in noise in bilateral cochlear implant users. The increase in the squelch effect suggests that binaural processing continue to adapt in the years following BiCI.

Strengths and weaknesses of this study

A major strength of this study is that we investigated a homogeneous group of patients because we used fixed inclusion criteria. In addition, for this study only simultaneously bilaterally implanted patients were included. A second strength is the lack of loss to follow-up, allowing comparison across years. A third strength is the use of variable SNRs instead of a fixed SNR which would have led to a ceiling effect.[24] A limitation of our study is that we did not control for binaural summation effects. Because binaural hearing is based on three principles, overlap in the effects is inevitable. By testing patients bilaterally and unilaterally with one cochlear implant switched off, a difference in loudness exists. Summation could have amplified the binaural squelch effect. However, summation causes louder speech and noise, therefore we feel that this potential

weakness is limited. In order to compensate for this limitation, patients were instructed to adjust the volume of their cochlear implant to the preferred level in the unilateral situation. Another limitation is that we did not control for different microphone settings among patients.

Future research

In the future, we will evaluate the development of a squelch effect in the group of sequentially implanted bilateral cochlear implant users after 2 years of follow-up.

CONCLUSION

This study shows that patients who underwent simultaneous BiCI developed a measurable benefit from the squelch effect after 2 years in their best performing ear and after 3 years in both ears separately. This effect increased over time. These observations suggest that the brain uses interaural differences to segregate sound from noise after simultaneous BiCI. The growth of the squelch effect over time suggest cortical integration and differentiation of inputs from bilateral cochlear implants due to continued binaural processes beyond the first years after implantation.

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CHAPTER

5

Comparison between simulated and actual unilateral hearing in sequentially implanted cochlear implant users, a cohort study

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ABSTRACT

Introduction

Previous studies have proven the effectiveness of bilateral cochlear implantation (BiCI) compared to unilateral cochlear implantation (UCI). In many of these studies the unilateral hearing situation was simulated by switching off one of the cochlear implants in bilateral cochlear implant users. In the current study we assess the accuracy of this test method. Does simulated unilateral hearing (switching off one cochlear implant) result in the same outcomes as real life unilateral hearing with one cochlear implant and a non-implanted contralateral ear?

Study design

We assessed the outcomes of one arm of a multicenter randomized controlled trial (RCT).

Methods

In the original trial, 38 postlingually deafened adults were randomly allocated to either simultaneous BiCI or sequential BiCI. In the current study we used the data of the sequentially implanted group (n=19). The primary outcome was speech perception in noise from straight ahead. Secondary outcomes were speech perception in silence, speech intelligibility in noise from spatially separated sources and localization capabilities. A within-subjects design was used to compare the results of hearing with one cochlear implant and a non-implanted contralateral ear (1-year and 2-year follow-up) with the results of switching off one cochlear implant after sequential bilateral implantation (3-year follow-up).

Results

We found no significant differences on any of the objective outcomes after 1-year, 2-year or 3-year follow-up.

Conclusion

This study shows that simulating unilateral hearing by switching off one cochlear implant seems a reliable method to compare unilateral and bilateral hearing in bilaterally implanted patients.

INTRODUCTION

Cochlear implantation (CI) has become a widely applied intervention in the treatment of patients with severe to profound bilateral sensorineural hearing loss (SNHL), who obtain limited benefit from conventional hearing aids. Although many patients with a single cochlear implant achieve high levels of speech perception-in-silence, even the most successful cochlear implantees experience difficulty with speech perception in noise and localization capabilities.[1,2]

In 2009, our study group started a randomized controlled trial (RCT) concerning the effectiveness of simultaneous bilateral cochlear implantation (BiCI) compared with either 1) unilateral cochlear implantation (UCI),[1,3] or 2) sequential BICI.[4] This RCT demonstrated a significant benefit of simultaneous BiCI compared with UCI after a 1- and 2-year follow-up period in everyday listening situations with speech and noise coming from different directions and for the ability to localize sounds.

Earlier (cohort) studies showed similar benefits of BiCI compared to UCI, however they used different methods to simulate the unilateral listening situation. In most of these studies, differences between bilateral and unilateral hearing were assessed using a within-subjects study design by switching off one cochlear implant in a group of bilaterally implanted patients and comparing the results with the bilateral listening situation.[5-13]

Our hypothesis was that this simulated unilateral listening situation would not be representative for an actual UCI situation. The electrode in a patient with bilateral implants would have diminished residual hearing. On the other hand, patients with bilateral implants are used to listening with two ears in everyday life, while in patients with a unilateral cochlear implant, patients may not have used one ear for an extensive period of time.

We performed the current study to assess the reliability of switching off one cochlear implant as a method to simulate unilateral hearing in bilateral cochlear implant users.

MATERIALS AND METHODS

Study design and participants

Data for the current study were collected as part of a multicenter RCT that compared simultaneous BiCI to sequential BiCI.[2-4]

This study was approved by the Human Ethics Committees of all participating centers (University Medical Centers of Utrecht, Maastricht, Nijmegen, Leiden and Groningen) (NL2466001808), registered in the Dutch Trial Register (NTR1722) and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

All participants eligible for CI were discussed in our cochlear implant team. Inclusion- and exclusion criteria were verified for each participant (Figure 1). After receiving informed consent and undergoing baseline hearing evaluations, patients were randomly allocated to either simultaneous BICI or sequential BiCI (Figure 1). All participants were implanted with Advanced Bionics HiRes90K® (Advanced Bionics, Sylmar, CA, USA) and used Harmony processors with HiRes/ HiRes120 processing strategies.

Logistics

In the current study, we will focus on the first implanted side (CI1) in the sequential BiCI group, by using a within-subjects design. Patients in this arm received their second cochlear implant 2 years after their first cochlear implant. Objective outcomes were measured after the first implantation at 1- and 2-years follow-up. After 2 years of follow-up, the patients received their second implant. In order to assess whether simulated unilateral hearing (switching off one cochlear implant) provides the same outcomes as real-life unilateral hearing, we compared the data of this group one year after unilateral implantation (1-year follow-up) with the situation after bilateral implantation (3-year follow-up), in which we switched off the second cochlear implant (CI2). As a sensitivity analysis, to correct for a possible learning effect with the first implanted ear, we also compared the unilateral 2-year follow-up data with the simulated unilateral 3-year data (switching off the second cochlear implant).

Outcome measures

The primary outcome was speech perception in noise from straight ahead, measured with the Utrecht-Sentence Test with Adaptive Randomized Roving levels (U-STARR) resulting in a speech reception threshold in noise (SRTn). A lower threshold value reflects better speech perception. A SRTn of 30 dB was considered speech perception in relative silence and was used as a cut-off point for all scores above 30 dB.

The other outcomes were 1) speech perception in silence, 2) speech intelligibility in noise from spatially separated sources (SISSS) and 3) localization capabilities. All these objective tests were conducted using the AB-york crescent of sound set-up. In previous articles of our study group more detailed information was presented about the test procedures and setup.

Speech perception in silence was measured using the standard Dutch consonant-nucleus-consonant (CNC) test. In the SISSS, in which the outcome is also expressed as an SRTn, sentences were presented from 60° azimuth to the left of the patient and noise from 60° azimuth to the right of the patient (S-60 N+60) or vice versa (S+60 N-60). When sounds come from different directions, participants usually have a best performing situation and a worst performing situation. In current study, in which we evaluate the unilateral group or situation, speech presented to the cochlear implant side was indicated as the best performing situation. If speech was presented to the contralateral ear and noise to the cochlear implant side we indicated this as the worst performing situation.

For the localization test, participants were instructed to face the loudspeaker in front of them during the entire procedure. Thirty phrases were presented randomly at 60, 65 or 70 dB SPL from one of the loudspeakers. The results were percentage correct responses in three localization conditions: 15° angle azimuth between five loudspeakers, 30° angle azimuth between five loudspeakers and 60° angle azimuth between three loudspeakers.

Data collection and statistical analysis

All gathered data were double-checked by two independent persons who did not have any further connections to the otorhinolaryngology department.

In order to compare baseline characteristics, means or medians were reported depending on normality of data. We used the Student *t* test for numeric normally distributed data, the Wilcoxon signed rank test for non-normally distributed data and the chi-square test for ordinal data.

Table 1. Patient characteristics

Characteristics	**Sequential BiCI (n=19)**
Gender, male:female	11:8
Age in years at CI	52.5 (12.5) [26-67]
Age in years at onset of severe hearing loss	
Right ear	30.5 (20.1) [3-55]
Left ear	30.6 (19.8) [3-55]
PTA (dB)	
Right ear	106 (12) [78-125]
Left ear	108 (13) [83-127]
Maximum phoneme score (%)	46.2 (20.4) [0-80]
Treatment hospital	
Utrecht	11
Maastricht	4
Nijmegen	2
Leiden	1
Groningen	1
Hearing aid use before CI	
Yes	19
No	0
Cause of deafness	
Hereditary	7
Unknown and progressive	9
Sudden Deafness	0
Head trauma	0
Meningitis	2
Rhesus antagonism	1
Sound exposure	0

Data are presented as mean (standard deviation) [range].
Abbreviations: BiCI, bilateral cochlear implantation; CI, cochlear implantation; PTA, pure-tone audiometry (average at 0.5, 1, and 2kHz).

RESULTS

Patient characteristics and missing data

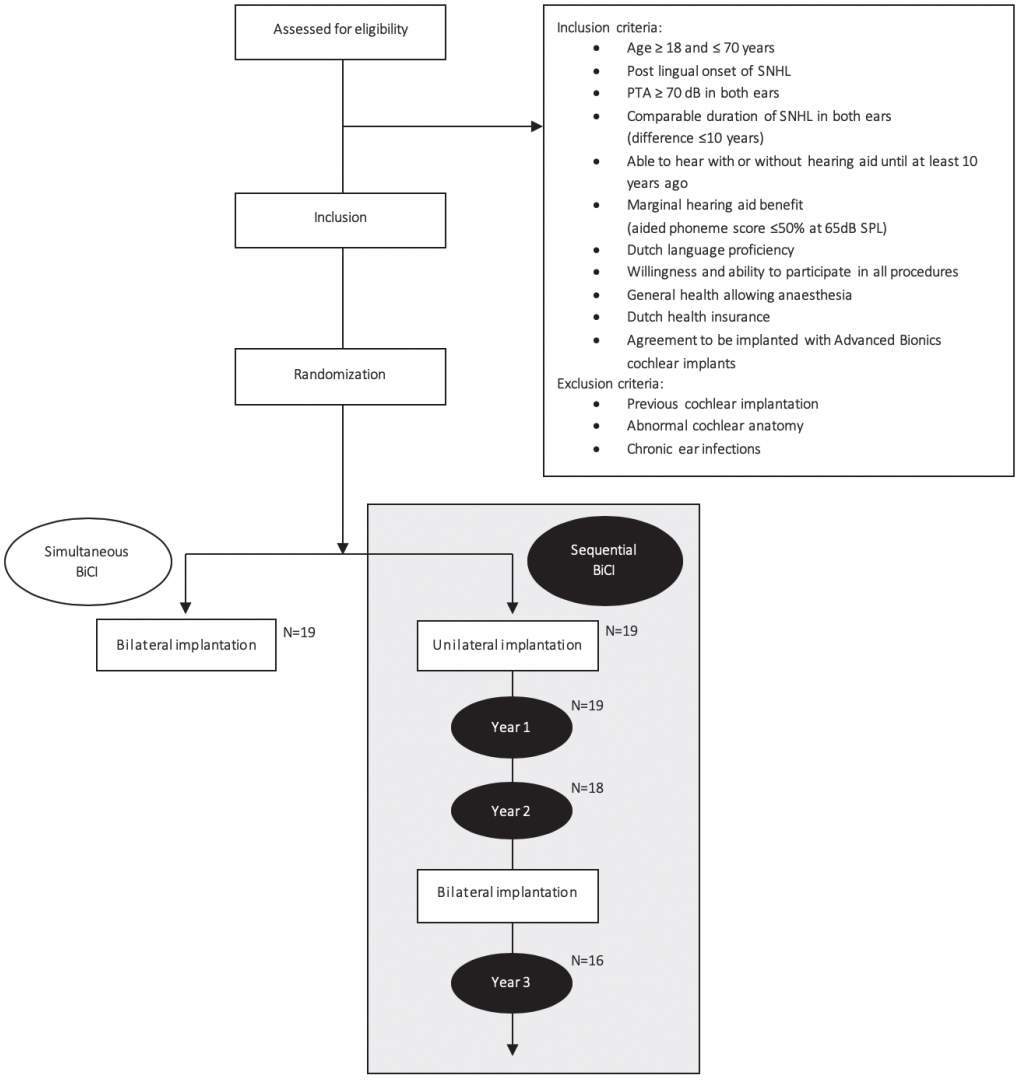
Between December 2009 and September 2012, a total of 19 participants were included in the sequential BiCI group. Figure 1 shows a flowchart of the study. Baseline characteristics are described in Table 1.

During the second and third year, two participants in the sequential BiCI group withdrew because of personal reasons. Another participant was excluded because of poor results with the first implant and low expectations after sequential implantation owing to central deafness caused by rhesus antagonism (Figure 1).

Objective results

We found no significant differences between simulated unilateral hearing (switching off one cochlear implant) 1 year after sequential BiCI and real life unilateral hearing 1 year and 2 years after UCI. The results of all outcomes separately are presented in Table 2.

Figure 1. Study flowchart



Abbreviations: BiCI, bilateral cochlear implantation; PTA, pure tone audiometry (average of 0.5, 1 and 2 kHz); SNHL; sensorineural hearing loss.

Table 2. Objective outcomes evaluating simulated and actual unilateral hearing

	Year 1 versus year 3			Year 2 versus year 3		
	Actual unilateral hearing	**Simulated unilateral hearing (switching off CI2)**	***P* value***	**Actual unilateral hearing**	**Simulated unilateral hearing (switching off CI2)**	***P* value***
	n=19	**n=16**		**n=18**	**n=16**	
Speech in noise both from straight ahead (SRTn in dB)	10.6 (1.6 –30.0)	10.0 (3.4 – 30.0)	NS	8.9 (2.2 – 30.0)	10.0 (3.4 – 30.0)	NS
Phoneme score in silence (CNC in %)	88.0 (64.0 – 98.0)	86.5 (42.0 – 98.0)	NS	85.0 (52.0 – 98.0)	86.5 (42.0 – 98.0)	NS
Speech in noise from spatially separated sources						
Best performing situation (SRTn in dB)	3.1 (-5.9 – 30.0)	5.1 (-5.3 – 30.0)	NS	3.8 (-5.6 – 30.0)	5.1 (-5.3 – 11.6)	NS
Worst performing situation (SRTn in dB)	16.9 (6.3 – 30.0)	18.4 (8.1 – 30.0)	NS	19.1 (4.1- 30.0)	18.4 (8.1 – 30.0)	NS
Localization of sounds						
60° (% correct)	40.0 (33.3 – 56.7)	41.7 (30.0 – 63.3)	NS	35.0 (23.3 – 53.3)	41.7 (30.0 – 63.3)	NS
30° (% correct)	23.3 (13.3 – 33.3)	23.3 (13.3 – 46.7)	NS	20.0 (13.3 – 33.3)	23.3 (13.3 – 46.7)	NS
15° (%correct)	20.0 (16.7 – 40.0)	20.0 (13.3 – 33.3)	NS	20.0 (10.0 – 40.0)	20.0 (13.3 – 33.3)	NS

Data are presented as median (range).

** Wilcoxon signed rank test.*

Abbreviations: CI2, second implanted ear in sequentially bilateral cochlear implant users; CNC, consonant-nucleus-consonant words; NS, not significant (P >0.05); SRTn, speech reception threshold in noise.

DISCUSSION

Key findings

In order to assess methodological issues with simulation of cochlear implant use, in present study we assessed whether simulated unilateral hearing (switching off one cochlear implant) provides the same outcomes as real life unilateral hearing.

Binaural hearing has been proven to be superior to unilateral hearing with regard to speech perception in noise and sound localization.[2,3,14-17] In previous studies, our study group concluded that there is a significant benefit of hearing with two implants compared to hearing with one implant in everyday listening situations in which speech and noise come from different directions.[2,3] Furthermore, bilaterally implanted patients are able to localize sounds, which is impossible for unilaterally implanted patients. Switching off one cochlear implant is an often-used method to assess the differences between uni- and bilateral hearing in bilateral implantees.[5-13] We assessed if this is a reliable test method.

However, the current study demonstrated similar results after UCI and hearing with one cochlear implant switched off after sequential BiCI on speech perception in silence, speech intelligibility in noise and localization tests.

Strengths and limitations

This is the first study that reports whether simulated unilateral hearing (switching off one cochlear implant) provides the same results as real life unilateral hearing.

A strength of our study is that we used a prospective within-subjects study design. All data were collected at fixed moments. Secondly, by measuring after a follow-up of at least 1 year after implantation, it was safe to assume that patients were used to their implants and that we had corrected for a possible learning effect. Furthermore, at time of inclusion, all patients suffered from profound sensorineural hearing loss (pure-tone average of greater than 90dB (threshold at 0.5, 1, 2, 3 kHz)). Because of the profound hearing loss in the contralateral ear (second implanted ear) patients were not used to listening with two ears after the first implantation. Therefore, the situation before the second implantation can be considered as actual unilateral hearing.

As this study was based on a secondary analysis from a larger RCT, a power analysis for the present study was not performed and the study may be underpowered.

CONCLUSION

We found no significant differences between simulated unilateral hearing (switching off one cochlear implant) and real life unilateral hearing. This study shows that simulating unilateral hearing by switching off one cochlear implant seems a reliable method to compare unilateral and bilateral hearing in bilaterally implanted patients.

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PART

TWO

FUTURE INDICATIONS

CHAPTER

6

The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: a systematic review

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ABSTRACT

Objectives

To present an overview of the effect of cochlear implantation (CI) on tinnitus in adults with bilateral sensorineural hearing loss (SNHL).

Data Sources

PubMed, Cochrane Library, CINAHL, and Embase databases were searched for articles from database inception up to January 13, 2015.

Methods

A systematic search was conducted. Original studies reporting on CI and the effect on tinnitus, measured with a tinnitus questionnaire, were included. The directness of evidence and risk of bias were assessed. Studies with a moderate or high directness of evidence and a low or moderate risk of bias were included for analysis. The pre- and postimplantation tinnitus scores were extracted.

Results

In total, 786 unique articles were retrieved. Although there was lack of high level of evidence studies, 10 articles satisfied the eligibility criteria. Overall, there was a reduction of mean tinnitus score. There was a decrease in tinnitus score in 25% to 72%, and a total suppression of tinnitus after implantation was reported in 8% to 45% of patients. Tinnitus was stable in 0% to 36% of patients, and increase of tinnitus occurred in 0% to 25%. Tinnitus induction rates in the patients without preoperative tinnitus varied from 0% to 10%.

Conclusions

There are no high level of evidence studies concerning CI and the effect on tinnitus. Overall, current literature shows that there is a decrease of mean tinnitus questionnaire score after unilateral CI. However, there is also a chance of increasing burden of existing tinnitus, and the induction of tinnitus is reported.

INTRODUCTION

Tinnitus is a disturbing phenomenon, with a high prevalence in sensorineural hearing-impaired patients. The prevalence rates in previous studies differ, ranging from 67% to 86% in cochlear implant candidates.[1] Unilateral cochlear implantation (UCI) is a common treatment for patients with bilateral sensorineural hearing loss (SNHL). An often reported additional benefit of this treatment is the subjective reduction of tinnitus.[1,2] Quaranta et al. showed total tinnitus suppression rates varying from 2% to 83%[1]. However, an increase of existing tinnitus, varying from 2% to 9% of patients, as well as a new onset of tinnitus, is described[1]. The induction of tinnitus occurs in 1% to 5% of patients according to recent studies describing the complications following CI[3,4]

Most studies that report on the effect of CI on tinnitus have been published in the last decade. However, a current systematic review of the literature following evidenced-based medicine (EBM) principles is still lacking.[1,5,6] Therefore, the objective of this study was to systematically review the effect of UCI and bilateral cochlear implantation (BiCI) on tinnitus in adults with bilateral SNHL.

METHODS

For this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement is used.[6]

Search strategy

A systematic search was performed in PubMed, Cochrane Library, CINAHL, and Embase databases from inception up to January 13, 2015. The search terms tinnitus and CI and all their synonyms were combined. Table 1 presents a complete overview of the search syntaxes.

Study selection

Two of the authors (G.G.J.R., A.V.Z.) independently screened the title and abstract for all of the retrieved articles, and subsequently they screened the full-text of eligible studies against the inclusion criteria. Original articles on CI and the effect on tinnitus in adults with bilateral SNHL were selected. Only studies in which tinnitus was evaluated with a questionnaire before and after implantation were included. Studies not on humans; written in languages

other than English, German, or Dutch; case reports (n<5); and studies with a non-retrievable abstract or full text were excluded. Furthermore, we excluded studies in which a cochlear implant was provided in an experimental setting. Disagreement between the authors was resolved by discussion (see Figure 1 for selection criteria).

Table 1. Search strategy (date of search January 13, 2015)

Database	Search	Syntax	Results
PubMed	#1	tinnitus[Title/Abstract]) OR tinnit*[Title/Abstract]) OR ringing[Title/Abstract]) OR booming[Title/Abstract]) OR buzzing[Title/Abstract] OR tinnitus[MeSH Terms]	465
	#2	((cochlear[Title/Abstract]) AND implant*[Title/Abstract]) OR (cochlear[Title/Abstract] AND prosthes*[Title/Abstract]) OR (cochlear[Title/Abstract] AND prosthesis[Title/Abstract] AND system[Title/Abstract]) OR (cochlear[Title/Abstract] AND prosthetic[Title/Abstract] AND devices[Title/Abstract]) OR (auditory[Title/Abstract] AND prosthes*[Title/Abstract]) OR CI[Title/Abstract]) OR implant*[Title/Abstract]) OR prosthes*[Title/Abstract]) OR "cochlear implants"[MeSH Terms]) OR "cochlear implantation"[MeSH Terms])	
	#3	#1 AND #2	
Cochrane	Modeled search strategy designed for Cochrane		174
CINAHL	Modeled search strategy designed for CINAHL		71
Embase	Modeled search strategy designed for Embase, not Medline		195

Assessing quality of studies

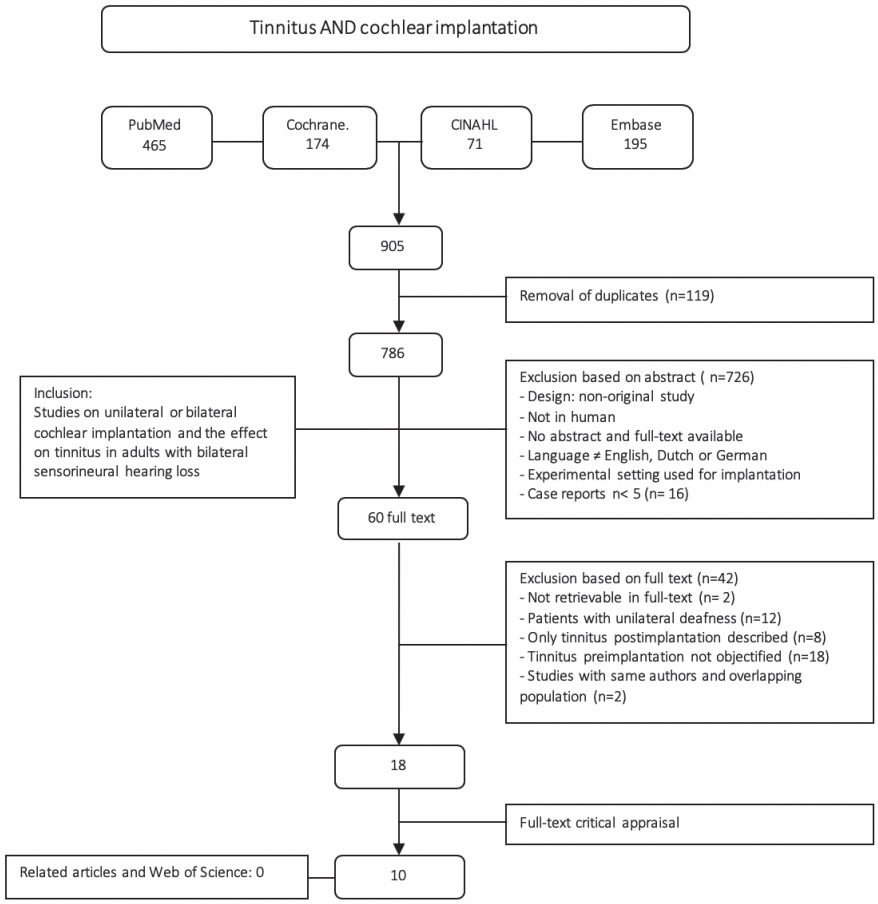
The directness of evidence and risk of bias were investigated by using predefined criteria by the previous mentioned two authors independently. A criterion was assessed as satisfactory, unsatisfactory, or unclear if it was not reported.

Assessing the directness of evidence involved evaluation of the study population, therapy, and reported outcome (refer to Table 2 for the criteria). A high directness of evidence was defined as a positive score on all the criteria, moderate directness was scored when the study met three out of the four criteria, and a low directness of evidence was scored if the study met less than three criteria.

The risk of bias was assessed by the evaluation of six criteria, based on The Cochrane Collaboration's tool for assessing risk of bias[7] and adapted to our needs: blinding, treatment allocation, standardization of therapy, standardization of outcome, selective reporting, and completeness of data. Studies were classified as having a low risk of bias when they met five or six criteria, as moderate if they complied with at least three criteria, and the remaining studies were classified as high risk of bias.

Discrepancies between the reviewers were discussed until consensus was reached. All studies with a low directness of evidence and/or a high risk of bias were excluded for further review.

Figure 1. Flowchart of study selection process



Data extraction

The same two authors extracted study characteristics and outcome data of the included studies. Our main outcome was the difference in pre- and postimplantation score, based on one or more of the tinnitus questionnaires. We extracted or computed the pre- and postimplantation scores based on the tinnitus questionnaires and the difference between these scores. Another outcome was the effect of CI on tinnitus in the individual patient, also based on tinnitus questionnaire scores. For this outcome, patients were classified in the following categories: total suppression, decrease, stable, and increase of tinnitus. When possible, data for newly induced tinnitus were also extracted.

Questionnaires

For all tinnitus questionnaires that were used to objectify tinnitus perception, a higher score meant a higher tinnitus burden. For the most commonly used questionnaire, the Tinnitus Handicap Inventory (THI), the total score represents the severity of the tinnitus as well: slight (0–16), mild (18–36), moderate (38–56), severe (58–76), or catastrophic (78–100).[8,9]

Meta-analysis

To find out whether a meta-analysis could be performed, we compared the study characteristics on heterogeneity and calculated the heterogeneity of effect size using Cochrane's I^2,using Review Manager (RevMan, version 5.3; The Cochrane Collaboration, London, United Kingdom).[10] We decided not to pool the data if I^2 was higher than 50%, because this corresponds to a notable heterogeneity.[11]

RESULTS

Search Strategy and Study Selection

Our search identified a total of 905 articles, of which 786 were unique. After screening of title, abstract, and full text, 768 articles were excluded using the EBM methodology. The remaining 18 articles were eligible for further analysis (Figure 1).[12–29]

Assessing quality of studies

The critical appraisal is presented in Table 2. The directness of evidence was found high in 12 studies[12,13,15,16,19–24,28,29] and moderate in 6 studies[14,17,18,25–27]. None of these studies had a low directness of evidence. All studies were prospective or retrospective case series.

In 10 studies[12,13,16,18,20–22,26,27,29] the risk of bias was moderate, and in eight studies[14,15,17,19,23–25,28] the risk of bias was high. Adequate randomization, treatment allocation, and blinding were not achieved in any of the included studies. Only one study scored unsatisfactory on standardization of therapy[17]. Two studies did not use a validated questionnaire to score the tinnitus perception[15,27]. One study did not report which questionnaire was used[17], and in three studies patients completed the questionnaires concerning preoperative tinnitus retrospectively[19,23,24]. Five studies gave an inadequate description of the inclusion and exclusion criteria of their study population[12,14,16,25,28]. In 11 studies[14,15,17,19,21–25,28,29] there was 10% or more missing data or the completeness of data was unclear. As a result, 10 studies with a moderate risk of bias and moderate or high directness of evidence remained for complete data extraction[12,13,16,18,20–22,26,27,29].

Data extraction

Large clinical heterogeneity between studies—such as differences between study designs, implant types, test conditions (cochlear implant on vs. cochlear implant off, implanted ear vs. contralateral ear vs. bilateral), follow-up duration, analyzed group, and outcome measures—and the lack of studies with a low risk of bias made it undesirable to pool the extracted data. This was confirmed by calculating the heterogeneity of effect size using Cochrane's I^2, for the studies using THI questionnaires. The I^2 was 78%, which means that there was substantial heterogeneity.[10,11] Therefore, we had to use descriptive analysis instead.

Study characteristics

Study characteristics are described in Table 3. The sample size of the study populations varied from 20 to 174 patients. Most studies included cochlear implant candidates with or without preoperative tinnitus. In three studies, only patients with bilateral hearing loss and preoperative tinnitus perception were included[12,27,29]. Mick et al.[21] compared the effect of CI in patients with Ménière's disease and matched controls. All other studies focused on patients with bilateral profound hearing loss without one specific cause.

All studies reported on unilateral implanted patients. In two of the included studies, all patients within the study received the same type of cochlear implant[18,29]. In the other studies, several brands and types of cochlear implants were used. For the measuring of tinnitus, six studies used the THI[12,13,16,18,21,26], one study used the Tinnitus Questionnaire (TQ)[22], and in six studies another type of questionnaire was used only or in combination with the THI or TQ[13,16,18,20,27,29].

Tinnitus questionnaire scores

Table 4 shows the outcome measures of the analyzed studies. All six studies that used the THI as an outcome measure found a significant reduction of the THI score after CI [12,13,16,18,21,26]. However, Mick et al.[21] found a significant reduction only in the Ménière group. Preimplantation scores ranged from 20.0 to 50.5. After CI all mean scores decreased, and the postimplantation scores varied from 7.0 to 32.3[12,13,16,18,21,26]. The study with the highest mean preoperative THI score also showed the largest mean reduction of 40.4 on the THI score[18]. The other studies showed a decrease in THI score varying from 13.6 to 19.5. The tinnitus evaluation plot in Figure 2 shows the pre- and postoperative THI scores for all individual studies. A significantly reduced postimplantation score was also seen in the study that used the TQ for the evaluation of tinnitus, with the score reduced from 30.9 to 23.6 after implantation[22]. Four studies[13,16,18,20] used a visual analogue scale (VAS) score for loudness of tinnitus. The preimplantation loudness score ranged from 5.4 to 6.3, with postimplantation scores varying from 1.4 to 2.8[13,16,18,20]. In two studies[13,18], the annoyance of tinnitus was scored in a VAS. The scores were 4.2 and 5.8 before implantation, with a significant reduction to 2.3 and 1.3, respectively, after implantation[13,18]. Some studies used other tinnitus questionnaires as outcome measures; they all reported a reduction after CI [18,27,28].

Table 2. Assessment of quality of included studies

Study	Sample size (n)	Study design	Directness of evidence: Patients	Therapy	Outcome	Follow up	DoE	Risk of bias: Blinding	Treatment allocation	Standardization (T)	Standardization (O)	Selective reporting	Complete data	RoB
Amoodi 2011	142	RCS	●	●	●	●	H	○	○	●	●	○	●	M
Bovo 2011	51	PCS	●	●	●	●	H	○	○	●	●	●	●	M
Daneshi 2005	20	PCS	●	●	●	○	M	○	○	●	●	○	?	H
Demajumdar 1999	99	PCS	●	●	●	●	H	○	○	●	○	●	?	H
Di Nardo 2007	30	PCS	●	●	●	●	H	○	○	●	●	○	●	M
Ito 1994	30	PCS	●	●	●	?	M	○	○	○	○	●	?	H
Kim 2013	35	RCS	●	●	●	○	M	○	○	●	●	●	●	M
Kloostra 2015	152	RCS	●	●	●	●	H	○	○	●	○	●	○	H
Kompis 2012	174	PCS	●	●	●	●	H	○	○	●	●	●	●	M
Mick 2014	40	RCS	●	●	●	●	H	○	○	●	●	●	○	M
Olze 2011	43	RCS	●	●	●	●	H	○	○	●	●	●	?	M
Olze, Gräbel 2012	40	RCS	●	●	●	●	H	○	○	●	○	●	?	H
Olze, Szczepek 2012	32	RCS	●	●	●	●	H	○	○	●	○	●	?	H
Pan 2009	244	PCS	●	●	●	?	M	○	○	●	●	○	○	H
Quaranta 2008	89	PCS	●	●	●	○	M	○	○	●	●	●	●	M
Ruckenstein 2001	38	PCS	●	●	●	?	M	○	○	●	○	●	●	M
Tyler 1995	82	PCS	●	●	●	●	H	○	○	●	●	○	○	H
Vallés-Varela 2013	20	RCS	●	●	●	●	H	○	○	●	●	●	?	M

Directness of evidence: *Patients: ● = patients with bilateral sensorineural hearing loss and tinnitus , ○ = other. Therapy: ● = unilateral or bilateral cochlear implantation, ○ = other. Outcome: ● = evaluation of tinnitus perception after implantation, ○ = no information about tinnitus. Follow-up: ● = ≥ 6 months, ○ = < 6 months. Level of directness of evidence: A high directness of evidence was defined as a positive score on all criteria, moderate as a positive score on three out of the four criteria, and a low directness of evidence if they complied with less than three criteria.* ***Risk of bias:*** *Blinding: ● = blinding of patient, researcher, observer; ○ = no blinding. Treatment allocation: ● = randomized or concealed, ○ = neither randomization nor concealment. Standardization of therapy (T): ● = implant type mentioned, ○ = not described or no standard protocol. Standardization of outcome (O): ● = the same validated tinnitus questionnaires were used to objectify tinnitus before and after implantation prospectively, ○ = no validated questionnaires used or not the same questionnaire before and after implantation or questionnaires for the preimplantation situation were completed retrospectively. Selective reporting: ● = well-defined and adequately described inclusion and exclusion criteria; ○ = inadequate description of sample selection. Completeness of outcome data: ● = <10% missing data, ○ ≥10% missing data. Level of risk of bias: Studies were classified as having a low risk of bias when they complied with six or five criteria, as moderate if they complied with at least three criteria, and the remaining studies were classified as high risk of bias. Abbreviations: ●, satisfactory; ○, unsatisfactory; ?, unclear; DoE, directness of evidence; H, high; M, moderate; PCS, prospective case series; RCS, retrospective case series; RoB, risk of bias.*

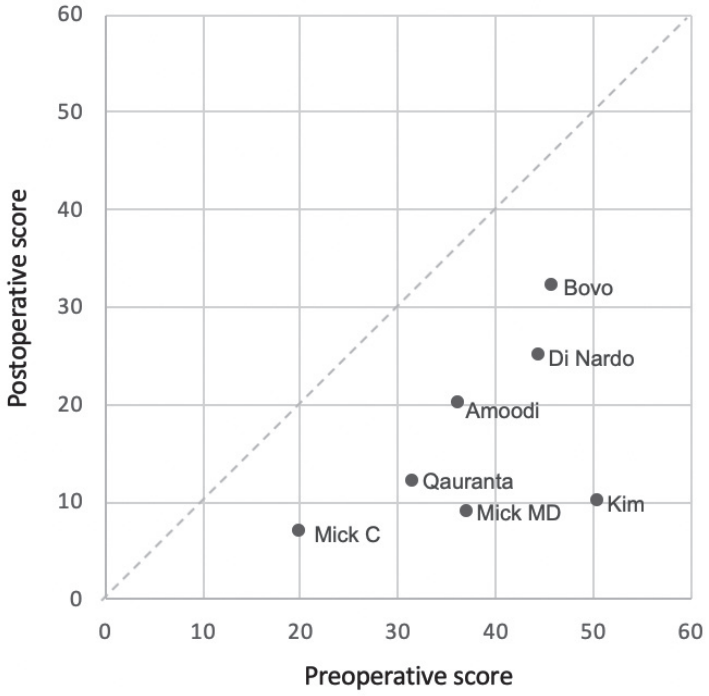
Table 3. Study characteristics

Study	Study design	Sample size, no.	Preoperative tinnitus, no.	Age, years (SD)	Implant indication	FU, mo	Implant type	Questionnaire
Amoodi 2011 Canada	RCS	142	142	54.2 (14.7)	Postlingual bilateral deafness, different causes	12	Advanced Bionics, Cochlear, Med-El	THI
Bovo 2011 Italy	PCS	51	36	46.0 (17.5)	Postlingual bilateral deafness, different causes	6	Advanced Bionics, Cochlear, Med-El	THI-Italian, Loudness VAS, Annoyance VAS
Di Nardo 2007 Italy	PCS	30	20	43.3 (15.8)	Postlingual bilateral deafness, causes not mentioned	6	Advanced Bionics, Cochlear, Med-El, Neurelec	THI, Loudness VAS, Annoyance (mild/ moderate/severe)
Kim 2013 South Korea	RCS	35	22	40.6 (17.5)	Profound bilateral sensorineural hearing loss	3 - 42	Cochlear	THI, Loudness VAS, Annoyance VAS, Effect on life VAS
Kompis 2012 Switzerland	PCS	174	125	51.2	NE	6	Advanced Bionics, Cochlear,Med-El,Neurelec	Loudness VAS, 10-Q
Mick 2014 Canada	RCS	MD: 20 C: 20	MD: 15* C: 6*	MD: 68.2 (11.6) C: 68.4 (11.2)	Ménière Other	12	Advanced Bionics, Cochlear, Med-El	THI
Olze 2011 Germany	RCS	43	39	51.7 (16.9)	Postlingual bilateral deafness, different causes	9 - 24	Cochlear, Med-El	TQ

Quaranta 2008 Italy	PCS	89	62	49.5†	Pre- and postlingual bilateral deafness, different causes	>3	Advanced Bionics, Cochlear, Med-El	THI
Ruckenstein 2001 USA	PCS	38	38	54 (13)	Bilateral deafness, causes not mentioned	NE	Advanced Bionics, Cochlear	Tinnitus rating scale‡
Vallés-Varela 2013 Spain	RCS	20	20	NE	Bilateral deafness, causes not mentioned	6 and 12	Cochlear	Modified THI, VAS

** There were tinnitus data available for these patients only. It is not clear whether the rest of patients did not suffer from tinnitus or this information is missing.*
†mean age of evaluated patients: only patients with bilateral tinnitus preoperative (n=41).
‡Tinnitus rating scale, score 1-5: 1= no tinnitus; 2= tinnitus present, not annoying; 3= tinnitus present, an annoyance but does not cause psychological distress; 4= tinnitus severe, causes distress but does not impair activities of daily living; 5= tinnitus debilitating.
Abbreviations: C; control; FU, follow-up; MD, Ménière's disease; NE, not extractable; PCS, prospective case series; RCS, retrospective case series; SD, standard deviation; THI, Tinnitus Handicap Inventory; TQ, Tinnitus Questionnaire; VAS, Visual Analogue Scale; 10-Q, 10-question tinnitus questionnaire.

Figure 2. Tinnitus Evaluation Plot for mean Tinnitus Handicap Inventory score per study.



Mick MD, patients in the study of Mick et al. with Ménière's disease; Mick C, control patients in the study of Mick et al.

Effect of cochlear implantation

In five of the studies that used the THI, some data about tinnitus suppression, decrease, stable, and increase rates were extractable or computable[12,13,16,18,26]. Total suppression of tinnitus according to the THI score was found in 30%[16] and 37%[12]. A decrease, but not total suppression, of the tinnitus was found in 29% to 72% of patients[12,13,16]. In 0% to 30% of patients, the tinnitus was stable, and an increase was found in 0% to 25%.[12,13,16,18] Quaranta et al. was the only study in which data in different conditions were extractable. Total suppression of bilateral tinnitus was present in 41% of patients when the cochlear implant was off and in 56% when the cochlear implant was on.[26] This study made a distinction between the implanted and contralateral ear as well, which resulted in a total suppression of tinnitus of 56% and 66% in the implanted ear with the cochlear implant off and on, respectively. In the contralateral ear, these

suppression rates were 54% and 66% in off and on conditions, respectively.[26] In the study of Vallés-Varela et al., the distinction between the implanted and contralateral ear was made as well, but different categories were used.[29] The authors found a quantitative improvement in the implanted ear in 65% and in the contralateral ear in 50% of patients[29].

In the study that used the TQ as an outcome measure, total suppression was seen in 8%. A decrease in TQ score was seen in 56% of the patients. The tinnitus score was stable in 36%, and in none of the patients was there an increase of tinnitus.[22]

Total suppression rates measured with other questionnaires than the THI and TQ ranged from 20% to 45%[13,16,20,27]. In 25% to 51% of patients there was a decrease[13,16,20,27]. In 5% to 25%[13,16,27] these scores were stable, and in 0% to 11% of the patients the scores increased decrease[13,16,20,27].

Overall, the total suppression rates from all the different questionnaires combined varied from 8% to 45%[12,13,16,20,22,27]. A decrease, without complete suppression of tinnitus, was seen in 25% to 72% of patients[12,13,16,20,22,27]. There was stable tinnitus in 0% to 36% and increasing scores in 0% to 25% of patients.[12,13,16,18,20,22,27]

In some of the studies, including patients with and without preoperative tinnitus, the development of newly induced tinnitus after CI could be studied. These induction rates varied from 0% to 10%.[18,20,26]

DISCUSSION

In this study, we described the results of a systematic review on the effect of CI on tinnitus in patients with bilateral SNHL. One finding is that the current best available evidence on this topic only consists of nonrandomized, low or moderate level of evidence studies, and there is lack of studies on BiCI.

The current review reports a decrease in mean tinnitus questionnaires scores after UCI in all analyzed studies where the primary outcome was extractable.[12,13,16,18,21,22,26,27,29] The overall total tinnitus suppression rates varied from 8% to 45% of patients after CI.[12,13,16,20,22,27] Decrease of tinnitus was seen in

25% to 72% of patients [12,13,16,20,22,27],and for 0% to 36% of the patients the tinnitus was stable. Increase of tinnitus occurred in 0% to 25% of patients.[12,13,16,18,20,22,27] The development of newly induced tinnitus after CI varied from 0% to 10% in the patients without preoperative tinnitus.[18,20,26]

The major strength of our study is that we present the first systematic review on this topic, which is characterized by a transparent search strategy, a transparent study selection process with strict inclusion and exclusion criteria, a transparent critical assessment of studies, and comprehensive outcome tables of all individual studies.

When interpreting the results, the following considerations need to be taken into account. Besides the lack of high-quality evidence, there was also large clinical heterogeneity between the studies. Pooling results from poor quality, nonrandomized study types is not recommended.[30]

All studies were retrospective or prospective case series[12,13,16,18,20–22,26,27,29], which means that all patients in these articles received treatment. These study designs are often used for studies on unintentional effects of an intervention.[30] In the included articles, the indication for CI in all patients was bilateral deafness, and change in tinnitus was the unintentional effect. Because of this, randomization and blinding were not achieved in all the studies. Moreover, blinding of observer and patient for CI is regarded as impossible.

The heterogeneity between the studies consisted of differences between study designs, implant types, test conditions, follow-up duration, analyzed groups, and outcome measures. In some of the retrospective studies, the design resulted in missing data or exclusion of patients with missing data, which led to smaller analyzed groups.[12,18,21,22] An additional weakness in some studies was the lack of information that is relevant for interpreting results and draw conclusions. For example, not all studies reported on the distinction between implanted and contralateral ear and differences between cochlear implant on and off conditions.[12,13,16,18,20–22,27]

The most used outcome measure in this review was the THI. This questionnaire is an internationally validated questionnaire developed by Newman et al.[8] Another often-used questionnaire for the evaluation of tinnitus is the TQ.[31] A problem with these and other tinnitus questionnaires is that they are not

validated to measure the effectiveness of therapies.[32] We had to exclude three studies where patients completed the questionnaires about the preoperative tinnitus perception retrospectively, because this is an unreliable method.[19,23,24]

All the reported tinnitus questionnaires are developed for tinnitus patients and not particularly for deaf or cochlear implant patients with tinnitus. The fact that there is no commonly accepted questionnaire to evaluate the effect of therapy on tinnitus has resulted in the use of various questionnaires, making comparison between studies difficult. The development of a questionnaire for this purpose is needed. Furthermore, randomized trials or well-defined prospective cohort studies are also needed to provide a higher level of evidence for the effect of CI in bilaterally deafened patients with tinnitus.

CONCLUSION

This systematic review provides an evaluation of current literature. Unfortunately, due to methodological considerations, no firm conclusions on the effectiveness of CI on tinnitus in adults with bilateral SNHL can be drawn. Existing literature reports a decrease of tinnitus after UCI. This suggests that CI be an effective treatment strategy for the reduction of tinnitus in this patient category. However, because an increase of tinnitus and newly induced tinnitus were also reported, a positive effect of CI on the individual patient experiencing tinnitus cannot be predicted for certain.

Table 4. Results

Study	Questionnaire	Analyzed group	Preimplant score, mean (SD)	Postimplantscore, mean (SD)	Difference score, mean (SD)	Statistics, P value	Effect on tinnitus in %(no.)				
							Total suppression	Decrease	Stable	Increase	Newly induced tinnitus, % (no.)*
Amoodi 2011	THI	Only patients with pre- and postoperative tinnitus (n=89)	36.3	20.2	-16.0 (2.3)	<.01	37%(53)	29%(41)	29% (41)	5%(7)	NA
Bovo 2011	THI-Italian,	Only patients with preoperative tinnitus (n=36)	45.9 (24.9)	32.3 (25.3)	-13.6	<.01	-	72%(26)	3%(1)	25%(9)	NA
	Loudness VAS		6.3 (2.3)	2.7 (2.8)	-3.6	<.01	36%(13)	42%(15)	17%(6)	6%(2)	NA
	Annoyance VAS		4.2 (2.0)	2.3 (2.1)	-1.9	<.01	31%(11)	44%(16)	14%(5)	11%(4)	NA
Di Nardo 2007	THI	Only patients with preoperative tinnitus (n=20)	44.5	25	-19.5	<.05	30%(6)	35%(7)	30%(6)	5%(1)	0%(0)
	Loudness VAS		5.9	2.8	-3.1	NE	40%(8)	25%(5)	25%(5)	10%(2)	
	Annoyance (mild/ moderate/ severe)		NE	NE	NE	NE	40%(8)	35%(7)	20%(5)	5%(1)	
Kim 2013	THI	Only patients with preoperative tinnitus (n=22)	50.5 (28.7)	10.1 (15.8)	-40.4	<.01	NE	NE	0%(0)	0%(0)	0%(0)
	Loudness VAS		5.4 (2.8)	1.4 (1.0)	-4.0	<.01	NE	NE	NE	NE	NE
	Annoyance VAS		5.8 (3.2)	1.3 (2.1)	-4.5	<.01	NE	NE	NE	NE	NE
	Effect on life VAS		6.0 (3.3)	1.1 (2.0)	-4.9	<.01	NE	NE	NE	NE	NE

Kompis 2012	Loudness VAS	Only patients with preoperative tinnitus (n=125)	NE	NE	NE	NE	20%(25)	28-51%	NE	7-9%	10%(5)
	10-Q		NE	NE	NE	NE					
Mick 2014	THI	NE	MD:37.0†	MD:9.0†	NE	MD: <.001	NE	NE	NE	NE	NE
			C:20.0†	C:7.0†	NE	C: .087	NE	NE	NE	NE	NE
Olze 2011	TQ	Only patients with preoperative tinnitus (n=39)	30.9 (18.8)	23.6 (15.8)	-7.3	<.01	8%(3)	56%(22)	36%(14)	0%(0)	0%(0)
Quaranta 2008	THI	Only patients with preoperative bilateral tinnitus (n=41) in different conditions‡	31.6 (24)	12.2 (20)	-19.4	<.01	CI on: 56%(23) CI off: 41%(14)	NE	NE	NE	6%(2)
Ruckenstein 2001	Tinnitus rating scale	Only patients with preoperative tinnitus (n=38)	3.8	1.8	-2.0	Significant: NE	45%(17)	50%(19)	5%(2)	0%(0)	NA
Vallés-Varela 2013	Modified THI	Only patients with preoperative bilateral tinnitus (n=20)	NE	NE	NE	NE	NE	NE	NE	NE	NA
	VAS		5.1 (1.9)§	3.3 (1.6)§	-1.8	NE	NE	NE	NE	NE	NA

**percentage of the patients without preoperative tinnitus.*
†median instead of mean.
‡conditions: implanted ear, contralateral ear, CI on, CI off.
§score for the ear with more intense tinnitus.
Abbreviations: C, control; CI, cochlear implant; MD, Ménière's disease; NE, not extractable; SD, standard deviation; THI, Tinnitus Handicap Inventory; TQ, Tinnitus Questionnaire; VAS, Visual Analogue Scale; 10-Q, 10-question tinnitus questionnaire; NA, not applicable.

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CHAPTER

7

Effect of unilateral and simultaneous bilateral cochlear implantation on tinnitus; a prospective study

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ABSTRACT

Objectives/hypothesis

To determine the effect of cochlear implantation (CI) on tinnitus perception in patients with severe bilateral postlingual sensorineural hearing loss (SNHL) and to demonstrate possible differences between unilateral cochlear implantation (UCI) and bilateral cochlear implantation (BiCI).

Study design

Prospective study.

Methods

Thirty-eight adult patients were included in this prospective study, as part of a multicenter randomized controlled trial (RCT) investigating the benefits of BiCI versus UCI. Pre- and postoperative tinnitus perception scores were evaluated, before and 1 year after implantation on three tinnitus questionnaires; the Tinnitus Handicap Inventory (THI), the Tinnitus Questionnaire (TQ) and a visual analogue scale (VAS) for tinnitus burden.

Results

Before implantation, the tinnitus prevalence was 42.1% (16 of 38) in the whole study group. One year after implantation, the tinnitus questionnaire scores had decreased in 71.4% according to the TQ and 80.0% according to the THI. Tinnitus was induced after CI in six patients, five in the bilateral and one in the unilateral group.

Conclusion

Our study shows that CI is effective in the reduction of tinnitus in patients with bilateral SNHL, who suffered from preoperative tinnitus. Conversely, tinnitus may also increase or even be induced by the CI itself. Cochlear implant candidates should be well informed about these possible consequences before undergoing surgery.

INTRODUCTION

Tinnitus is defined as an acoustic sensation in the absence of an external sound.[1] The prevalence of tinnitus in adults is high and increases with age.[2] Millions of people around the world experience chronic tinnitus, with estimates between 6% and 20% in the general population.[3] In 1% to 3% of these cases, tinnitus will severely affect quality of life.[1,3] There is a strong association between tinnitus and sensorineural hearing loss (SNHL).[2] In profoundly hearing-impaired patients, the prevalence of tinnitus is even higher, and it reaches 67% to 86% in cochlear implant candidates.[4]

Cochlear implantation (CI) has become standard treatment in the Western world for patients with severe to profound bilateral hearing loss, who no longer derive benefit from hearing aids.[5,6] In 1981, House and Brackmann described a suppressive effect of CI on tinnitus.[7] Suppression rates of tinnitus after CI vary widely from 8% to 61%.[6,8-13] Rates for a decrease in tinnitus perception are even higher and vary from 64% to 100%.[6,8,10-13] Nevertheless, an increase of tinnitus perception or even new onset of tinnitus perception after cochlear implant surgery is also described. Recent studies on overall complications of CI reported new onset tinnitus in 1.3% to 4.9% of patients.[14,15] A retrospective study on tinnitus distress in unilateral cochlear implant patients showed that tinnitus can be a major problem, as 24.5% of the surveyed patients reported moderate to severe newly developed tinnitus after implantation.[16]

As described above, current literature about the relationship between tinnitus and CI is inconclusive and there is a high risk of bias due to the fact that most are retrospective studies. Therefore there is a need for good quality studies to increase the evidence base on possible effects on tinnitus. Even less is known about bilateral CI and its effect on tinnitus perception. In the present prospective study, we aim to evaluate the effect of CI on tinnitus perception, after UCI or simultaneous BiCI.

MATERIALS AND METHODS

Study design and participants

Our study was embedded in a multicenter randomized controlled trial (RCT) on the benefits of simultaneous bilateral cochlear implantation (BiCI) compared to unilateral cochlear implantation (UCI) in adults with severe bilateral postlingual sensorineural hearing loss.

This trial was designed and coordinated by the University Medical Center (UMC) Utrecht in collaboration with UMC Groningen, Leiden UMC, Maastricht UMC and Radboud UMC. The study was approved by the Human Ethics Committees of all participating centers (NL2466001808) and registered in the Dutch Trial Register (NTR1722). All patients eligible for CI in the five collaborating centers were discussed and in- and exclusion criteria were verified for each patient. Between January 2010 and September 2012, we included 38 adults in the study. Using a web-based randomization program, subjects were randomized to either 1) UCI or 2) simultaneous BiCI. All patients were implanted with Advanced Bionics HiRes90K® implants. The use of a contralateral hearing aid was encouraged for the unilateral implantees. Evaluations took place preoperatively and 1 year after implantation.

Questionnaires

All patients were asked to complete three questionnaires concerning tinnitus perception before and 1 year after implantation: the Tinnitus Handicap Inventory (THI), the Tinnitus Questionnaire (TQ) and a visual analogue scale on tinnitus burden (VAS). The first two are internationally validated questionnaires.

The THI comprises a 12-item functional subscale, an 8-item emotional subscale and a 5-item catastrophic subscale. The three answer possibilities are “yes”, “sometimes” and “no”, with scores of 4, 2 and 0 respectively.[17] The total score of this questionnaire represents the severity of the tinnitus: slight (0-16), mild (18-36), moderate (38-56), severe (58-76) or catastrophic (78-100).[17,18] The TQ consists of 52 questions on emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance and somatic complaints. The alternatives to respond are “true”, “partly true” and “not true”, and correspond to scores of 2, 1 and 0. Forty out of these 52 questions are used for the total TQ score.[19] All questionnaires were available in Dutch and for all of them; a higher score meant a higher tinnitus burden. The VAS is a continuous scale on which

patients could rate the overall tinnitus nuisance over the last week, ranging from 0 to 10.[20]

When a patient did not suffer from tinnitus preoperatively or 1 year after implantation, they still received all the tinnitus questionnaires. These patients were asked to answer that the questionnaires were not applicable for them at that time point.

Statistical analysis

For all patients pre- and postoperative tinnitus questionnaire scores were computed. We performed analyses to evaluate tinnitus perception in patients with preoperative tinnitus and in patients with newly induced tinnitus after CI. Furthermore, we compared the unilateral with the bilateral implanted group to identify potential differences in tinnitus perception.

Tinnitus questionnaire results of patients without tinnitus perception were scored as 0. If 10% or more of the questions within the THI or TQ were not completed, patients were excluded from further analysis of that questionnaire. In case of missing data between 0% and 10%, the total score of the THI or TQ was calculated based on the total score of the completed questions. For the VAS, which only consists of one question, a complete case analysis was performed.

Normal distribution was checked with the Kolmogorov-Smirnov test. Because none of the results were normally distributed we used medians and non-parametric tests for the analysis. For comparison of baseline characteristics between the groups with and without preoperative tinnitus perception, we used the Fisher's exact test and Mann-Whitney *U* test. To compare the pre- and postoperative scores on the tinnitus questionnaires we used the Wilcoxon signed rank test. For the comparison between the uni- and bilateral group, we used the Mann-Whitney *U* test. The difference in prevalence of newly induced tinnitus between the uni- and bilateral group was tested with the Fisher's exact test. For all above mentioned analyses, $P < 0.05$ was considered as significant.

We also analyzed and compared pre- and postoperative scores based on the internationally validated THI and TQ, to divide patients into six categories according to the effect of CI on tinnitus perception: 1) decrease, 2) increase, 3) total suppression, 4) stable, 5) induction, and 6) no tinnitus pre- and postoperative. In a scatterplot, we evaluated pre- and postoperative scores

for each individual patient with preoperative tinnitus perception (the Utrecht Tinnitus Evaluation Plot [UTEP]). We analyzed THI and TQ separately because they measure the tinnitus burden in a different way. A patient was considered to have tinnitus when a score higher than zero was reached on either one of these questionnaires. All data were analyzed using SPSS for Windows version 20.0 (Armonk, NY:IBM).

RESULTS

All included patients completed the three different tinnitus questionnaires preoperatively and 1 year after implantation. The VAS score was missing in two patients before implantation and in two patients after implantation. These four patients were excluded for the analysis of the VAS score only. There were no missing data in the THI before implantation; after implantation, one patient did not complete one question. For the TQ there was one patient who did not complete four questions before implantation, after implantation there were no missing data.

All patients were regular cochlear implant users. Twelve out of 19 patients in the unilateral group used a contralateral hearing aid after 1 year of follow-up. Sixteen of the 38 patients (42.1%) involved in the trial reported tinnitus perception before CI. Baseline characteristics of all patients are summarized in Table 1. There were no statistical differences in baseline characteristics between the patients with and without preoperative tinnitus perception.

Effect of cochlear implantation in patients with preoperative tinnitus perception

Figure 1 demonstrates the differences in tinnitus perception, based on the validated THI and TQ questionnaires before and 1 year after implantation for patients with preoperative tinnitus. Thirteen patients had a preoperative score higher than zero on both questionnaires. Two patients scored positive for tinnitus on the THI score only, and one patient on the TQ only. This means that 16 patients had a positive score for tinnitus at least on one of the two questionnaires.

Table 1. Preoperative baseline characteristics

Characteristics	Preoperative (n=38)
Gender, male:female	19:19
Age in years at first CI	50.3 (14.4)
Age in years at onset of hearing loss	
Right ear	24.2 (19.5)
Left ear	24.1 (19.3)
Age in years at start of severe hearing loss/ hearing aid use	
Right ear	30.7 (18.4)
Left ear	30.3 (18.4)
Mean duration of severe hearing loss before CI in years	19.9 (13.9)
Hearing aid use before CI	
Yes	34
No	4
Cause of deafness	
Hereditary	16 (42.1)
Unknown and progressive	15 (39.5)
Sudden Deafness	2 (5.3)
Head trauma	1 (2.6)
Meningitis	2 (5.3)
Rhesus antagonism	1 (2.6)
Sound exposure	1 (2.6)

Data are presented as mean (standard deviation) unless otherwise noted.
Abbreviations: CI, cochlear implantation; PTA, pure-tone audiometry (average at 0.5, 1, and 2kHz).

One year after implantation, the THI scores had decreased in 80.0% (12 of 15) of patients, of whom four patients (26.7%) were completely free of tinnitus. Progression of tinnitus occurred in only one patient, and two patients were stable in THI scores. None of the patients had severe or catastrophic tinnitus according to the THI score. The UTEP in Figure 2 shows the pre- and postoperative scores on the THI for each individual patient. The two patients with the highest preoperative scores had a moderate severity score before, and this decreased to mild tinnitus perception after implantation. Five patients experienced mild tinnitus before implantation, and eight patients only had slight tinnitus severity preoperatively.

According to the TQ scores, 71.4% (10 of 14) of patients had a decrease in score, of whom two patients were completely free of tinnitus. Increase in TQ score occurred in three patients and one patient had an unchanged score. Figure 3 shows the UTEP according to the TQ.

Table 2 shows the scores on the three different tinnitus questionnaires before and after CI for the patients with preoperative tinnitus. The mean scores of all three questionnaires were significantly lower after implantation.

Figure 1. Differences in tinnitus perception before and 1 year after cochlear implantation in patients with preoperative tinnitus (n=16), based on the Tinnitus Handicap Inventory (THI; n=15) and Tinnitus Questionnaire (TQ; n=14)

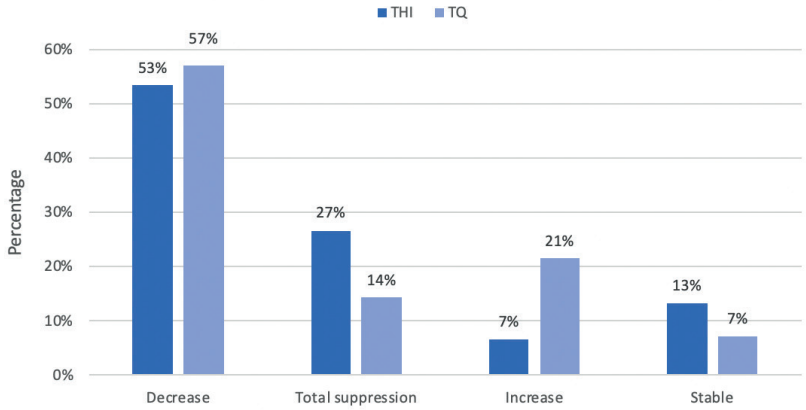


Table 2. Tinnitus questionnaire scores before and 1 year after cochlear implantation in patients with preoperative tinnitus perception

	Preimplantation	Postimplantation	*P* value *
Overall THI score	13.0 (0-48])	3.0 (0-28)	<0.01[a]
Functional subscale	10.0 (0-28)	2.0 (0-16)	0.00
Emotional subscale	1.0 (0-16)	0.0 (0-10)	0.03[a]
Catastrophic subscale	2.0 (0-8)	0.0 (0-8)	NS
Overall TQ score	17.0 (0-41)	7.0 (0-26)	0.02[a]
Emotional distress subscale	2.5 (0-17)	1.5 (0-8)	NS
Auditory perceptual difficulties subscale	3.5 (0-14)	0.5 (0-9)	NS
Intrusiveness subscale	5.0 (0-10)	2.5 (0-7)	0.03[a]
Sleep disturbance subscale	1.0 (0-6)	0.0 (0-7)	NS
Somatic complaints subscale	2.0 (0-3)	0.0 (0-2)	0.01[a]
VAS score	5.0 (0-10)	2.0 (0-7)	0.04[a]

Data are presented as median (range).
** Wilcoxon signed rank test. [a] = significant (P < 0.05). Abbreviations: NS, not significant (P > 0.05); THI, Tinnitus Handicap Inventory; TQ, Tinnitus Questionnaire; VAS, visual analogue scale of tinnitus burden.*

Figure 2. Utrecht Tinnitus Evaluation Plot for pre- and postoperative Tinnitus Handicap Inventory (THI) score per patient

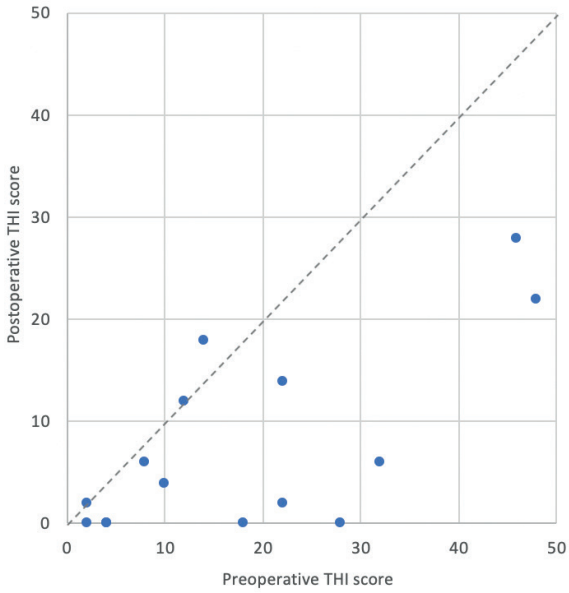
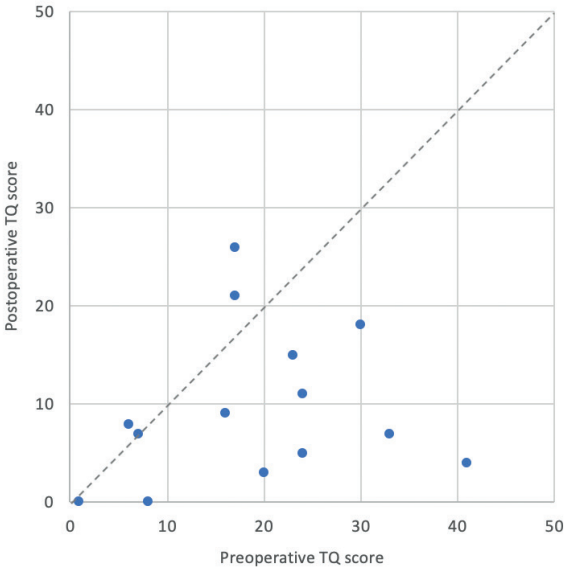


Figure 3. Utrecht Tinnitus Evaluation Plot for pre- and postoperative Tinnitus Questionnaire (TQ) score per patient



Newly induced tinnitus after cochlear implantation

Tinnitus was induced after CI in 27.3% (6 of 22) of patients who did not suffer from tinnitus preoperatively. An induction was measured according to both questionnaires in four patients, according to the THI in one patient and in two patients according to the TQ only. One of these patients, who had induction of tinnitus according to the TQ score, had a positive score on the THI questionnaire preoperatively. This means that this patient already experienced tinnitus before implantation, therefore we did not count this patient in the category induction of tinnitus after implantation.

According to the THI questionnaire, two patients with newly induced tinnitus suffered from tinnitus with a moderate severity, one patient with a mild severity and two patients had a slight severity of tinnitus. Table 3 shows the scores on the three different tinnitus questionnaires 1 year after implantation.

Table 3. Postoperative tinnitus questionnaire scores in patients with newly induced tinnitus

	Postimplantation (n=6)
Overall THI score	23.0 (0-52)
Functional subscale	14.0 (0-22)
Emotional subscale	4.0 (0-18)
Catastrophic subscale	5.0 (0-12)
Overall TQ score	17.5 (0-44)
Emotional distress subscale	4.5 (0-18)
Auditory perceptual difficulties subscale	4.0 (0-10)
Intrusiveness subscale	4.5 (0-10)
Sleep disturbance subscale	1.0 (0-5)
Somatic complaints subscale	1.5 (0-4)
VAS score	4.0 (1-9)

Data are presented as median (range).
Abbreviations: THI, Tinnitus Handicap Inventory; TQ, Tinnitus Questionnaire; VAS, visual analogue scale of tinnitus burden.

Differences between unilateral and bilateral cochlear implantees

In our study design, patients were randomized before treatment. Of all the patients with preoperative tinnitus, seven were allocated to the unilateral group (36.8%) and nine were allocated to the bilateral group (47.4%).

One year after implantation we observed a significant decrease of tinnitus measured with the THI questionnaire in both uni- (P = 0.03) and bilaterally implanted patients (P = 0.05). In addition, we measured a significant decrease in TQ score (P = 0.04) in the bilaterally implanted patients.

The prevalence of newly induced tinnitus was 50.0% (5 of 10) in the simultaneous BiCI group compared to 8.3% (1 of 12) in the UCI group, this difference was not statistically significant (P = 0.06).

Table 4. Differences in tinnitus perception between unilateral and bilateral cochlear implantation

	Study group	Preimplantation	*P* *	Postimplantation	*P* *	*P* **
Overall THI score	Unilateral	8.00 [2-32]	NS	2.0 [0-6]	NS	0.03[a]
	Bilateral	22.00 [0-48]		12.0 [0-28]		0.04[a]
Functional subscale	Unilateral	4.0 [2-24]	NS	2.0 [0-6]	NS	0.03[a]
	Bilateral	12.0 [0-28]		2.0 [0-16]		0.02[a]
Emotional subscale	Unilateral	0.0 [0-4]	NS	0.0 [0-0]	NS	NS
	Bilateral	4.0 [0-20]		0.0 [0-10]		NS
Catastrophic subscale	Unilateral	0.0 [0-4]	NS	0.0 [0-2]	NS	NS
	Bilateral	4.0 [0-8]		2.0 [0-8]		NS
Overall TQ score	Unilateral	7.0 [0-33]	NS	7.0 [0-21]	NS	NS
	Bilateral	20.0 [1-41]		9.0 [0-26]		0.04[a]
Emotional distress subscale	Unilateral	2.0 [0-6]	NS	0.0 [0-8]	NS	NS
	Bilateral	4.0 [0-17]		2.0 [0-7]		NS
Auditory perceptual difficulties subscale	Unilateral	3.0 [0-14]	NS	1.0 [0-9]	NS	NS
	Bilateral	4.0 [0-13]		0.0 [0-5]		NS
Intrusiveness subscale	Unilateral	2.0 [0-10]	NS	2.0 [0-5]	NS	NS
	Bilateral	6.0 [1-7]		3.0 [0-7]		NS
Sleep disturbance subscale	Unilateral	0.0 [0-6]	NS	0.0 [0-2]	NS	NS
	Bilateral	2.0 [0-4]		0.0 [0-7]		NS
Somatic complaints subscale	Unilateral	0.0 [0-3]	NS	0.0 [0-2]	NS	NS
	Bilateral	2.0 [0-3]		0.0 [0-1]		0.02[a]
VAS score	Unilateral	4.0 [0-7]	NS	1.5 [0-5]	NS	NS
	Bilateral	5.0 [0-10]		3.0 [0-7]		NS

*Data are presented as median [range]. * Mann-Whitney U test for comparison of unilateral versus bilateral cochlear implantation. ** Wilcoxon signed rank test for comparison of preimplantation versus postimplantation scores; [a] = significant (P < 0.05).*
Abbreviations: NS, not significant (P > 0.05); THI, Tinnitus Handicap Inventory; TQ, Tinnitus Questionnaire; VAS, visual analogue scale of tinnitus burden

DISCUSSION

In this study, we evaluated the effect of CI on tinnitus perception in patients with severe bilateral postlingual sensorineural hearing loss. All patients entered this study for the hearing restoration and none of the patients were included into the study for tinnitus treatment perse. The prevalence of preoperative tinnitus in our population was 42.1%, which is lower than described in a previous study, that report a prevalence of 67% to 86% in cochlear implant candidates.[4] We could not give a clear reason for this finding.

One year after implantation, the tinnitus questionnaire scores had decreased in most patients and some patients had become completely free of tinnitus. The UTEP showed that the highest preoperative severity category according to the THI was moderate in two patients, both of whom decreased to slight tinnitus perception after implantation. Overall, scores on the THI, TQ and VAS had decreased significantly 1 year after implantation, compared to preimplantation. In 71.4% of patients tinnitus decreased according to the TQ and in 80.0% according to the THI. These results are comparable with the results described in previous literature, which describe a large variation in tinnitus reduction varying from 64% to 100%.[6,8,10-13] It needs to be noted that only few were prospective studies and none were randomized into unilateral or bilateral implanted groups.

Recent studies reported the induction of tinnitus after CI. Incidence rates vary widely ranging from 1.3% to 24.5%.[14-16,21] One would expect, having used soft surgery techniques in all of our patients, that the percentage of induced tinnitus would be low, however we still encountered newly reported tinnitus in 27.3% (6 of 22). Thus, even with the evolving of surgical CI techniques we still seem unable to avoid tinnitus induction in some patients. The electrode of the Advanced Bionics implant is small; however the newer electrode designs may facilitate soft surgery even more.[22]

One of the findings of our study is the discrepancy between the THI and TQ questionnaires. Both questionnaires are validated but nonetheless in nine patients there were differences in tinnitus severity findings between the two questionnaires. This finding is supported by another publication that also showed a discrepancy between the two questionnaires; the authors concluded that both questionnaires broadly measure tinnitus severity similarly, but small differences between questionnaires led to these discrepancies.[23]

The existing literature is not conclusive on the effect of bilateral CI on tinnitus. Contradictory results were found; Summerfield et al.[24] reported an increase in tinnitus annoyance after the insertion of a second implant in their RCT, while Olze et al.[25] reported a decrease in tinnitus annoyance after the first CI and an additional decline after insertion of the second implant. In the current RCT, we reported a substantial higher incidence of newly developed tinnitus in the bilateral group compared to the unilateral group (5 versus 1 patient), however this difference was not statistically significant ($P = 0.06$), probably due to the small sample size.

The major strength of our study is that we used a prospective study design to evaluate potential changes in tinnitus perception preoperatively and 1 year after CI. Our study design has an intrinsic reduced risk of bias compared to other study designs. Secondly, by measuring at a follow-up of 1 year, it is safe to assume that hearing and tinnitus suppression has mostly stabilised in our patient groups. Thirdly, our study allowed us to investigate the effects of unilateral versus simultaneous BiCI on tinnitus perception.

Due to the primary aim of our study was to evaluate the hearing results of unilateral compared to simultaneous bilateral implantation we have not selected patients solely for the presence of tinnitus. In the whole study group of 38 patients, only 16 had preoperative tinnitus. Therefore our total tinnitus group had a limited size. Furthermore, some patient characteristics concerning tinnitus were missing (e.g., side of tinnitus and effect of on- and off modus of the CI or hearing aid on tinnitus perception). Therefore we could not determine correlations between some patient related factors and there potential effect on tinnitus perception. Since hearing aids can affect tinnitus perception, the use of hearing aids preoperatively and contralateral use of a hearing aid in the unilateral group postoperatively, could have contributed to the reported results.

In conclusion, we have shown that CI is an effective treatment for tinnitus reduction in most of our cochlear implant candidates, who suffer from slight to moderate tinnitus preoperatively. Because newly induced tinnitus was also reported in a number of patients, all cochlear implant candidates should be informed about the occurrence of newly induced tinnitus as a possible complication. In our study we report more frequent occurrence of newly induced tinnitus in the bilateral group, although this was not statistically significant. There is some uncertainty due to the sample size of our study population.

CONCLUSION

The current study shows that CI is effective in the reduction of tinnitus in patients with bilateral sensorineural hearing loss, who suffer from slight to moderate preoperative tinnitus. However, tinnitus may also be increased or even induced by CI. Cochlear implant candidates should be well informed about these possible consequences before undergoing surgery, although most report a benefit.

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CHAPTER

8

Cochlear implantation for patients with single-sided deafness or asymmetrical hearing loss: a systematic review of the evidence

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ABSTRACT

Objective

A systematic review of the literature to evaluate the clinical outcome of cochlear implantation (CI) for patients with single-sided deafness (SSD) or asymmetrical hearing loss (AHL).

Data sources

We searched the PubMed, Embase, Cochrane Library, and CINAHL databases from their inception up to December 10, 2013 for SSD or AHL and CI or their synonyms.

Study selection

In total, 781 articles were retrieved, of which 15 satisfied the eligibility criteria. Our outcomes of interest were speech perception in noise, sound localization, quality of life (QoL), and tinnitus.

Data extraction

Critical appraisal showed that six studies reported on less than five patients or that they carried a low directness of evidence or a high risk of bias. Therefore, we extracted the data of nine studies (n = 112). Patient numbers, age, duration of deafness, classification of deafness, pure tone audiometry, follow-up duration and outcome measurements were extracted from all nine articles.

Data synthesis

Because of large heterogeneity between studies, we were not able to pool data in a meta-analysis. We therefore summarized the results of the studies specified per outcome.

Conclusion

There are no high-level-of-evidence studies concerning CI in patients with SSD or AHL. Current literature suggests important benefits of CI regarding sound localization, QoL and, tinnitus. Varying results were reported for speech perception in noise, possibly caused by large clinical heterogeneity between studies. Larger and high-quality studies are certainly warranted.

BACKGROUND

Single-sided deafness (SSD) is defined as a condition in which an individual has non-functional hearing on one side and normal hearing on the contralateral side. Patients who develop SSD become aware of the importance of binaural hearing in their daily life in terms of social interaction and communication.[1]

Binaural hearing has been proven to be superior to unilateral hearing with regard to speech perception in noise and sound localization.[2-5] The advantages that normal-hearing listeners gain from binaural hearing are based on three principles: 1) the squelch effect (ability of the brain to separate sound and noise signals from spatially separated sources),[4,6] 2) the binaural summation effect (redundancy of auditory input)[7] and 3) the head shadow effect (better signal to noise ratio).[8]

Current clinical practice for patients with SSD consists of optimizing hearing with either a Contralateral Routing of Signal (CROS) or a Bone Conduction Device (BCD). Both devices are effective in addressing the head shadow effect and thus restoring sound awareness to the deaf side, but they do not provide bilateral auditory input, which is needed for actual binaural hearing.

The limitations of CROS or BCD may be overcome by providing a cochlear implant. During the last decades, cochlear implantation (CI) has become a widely accepted intervention for patients with bilateral sensorineural hearing loss (SNHL) and the selection criteria for implantation have been broadened. Recently, Van Schoonhoven et al. reviewed current literature on bilateral cochlear implantation (BiCI) and concluded that patients with bilateral SNHL perform better on sound localization tests when patients were implanted bilaterally compared to unilaterally.[9]

According to these findings in bilateral deaf patients, the hypothesis is that due to the restored bilateral auditory input, spatial hearing will also improve after CI in patients with unilateral deafness, including patients with SSD or asymmetrical hearing loss (AHL). Next to these audiological benefits, CI may result in suppression of tinnitus.[10]

Until now, the clinical outcome of CI for patients with SSD or AHL has not been reviewed systematically in detail.

METHODS

This systematic review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, a 27-item checklist to assure clear and transparent reporting of systematic reviews.[11,12]

Search strategy

A systematic search in the PubMed, Embase, Cochrane Library and CINAHL databases was conducted on December 10th, 2013. The main search terms were SSD or AHL and CI and their synonyms (see Table 1 for complete syntaxes). To minimize reporting and retrieval bias, no terms related to our outcome were included in the search. In addition, a cross-reference and related article search was performed.

Table 1. Search syntax (date of search: December 10, 2013)

Database	Search	Syntax	Results
PubMed	#1	single-sided[tiab] OR one-sided[tiab] OR unilateral*[tiab] OR asymmetric*[tiab] OR monaural*[tiab])	352
	#2	deaf*[tiab] OR "loss of hearing"[tiab] OR (hearing[tiab] AND (impair*[tiab] OR loss[tiab] OR disorder*[tiab]))	
	#3	cochlear implant*[tiab]	
	#4	#1 AND #2 AND #3	
Embase	Modeled search strategy designed for Embase, in Title/Abstract field		338
Cochrane	Modeled search strategy designed for Cochrane, , in Title/Abstract field		15
CINAHL	Modeled search strategy designed for CINAHL, , in Title/Abstract field		76

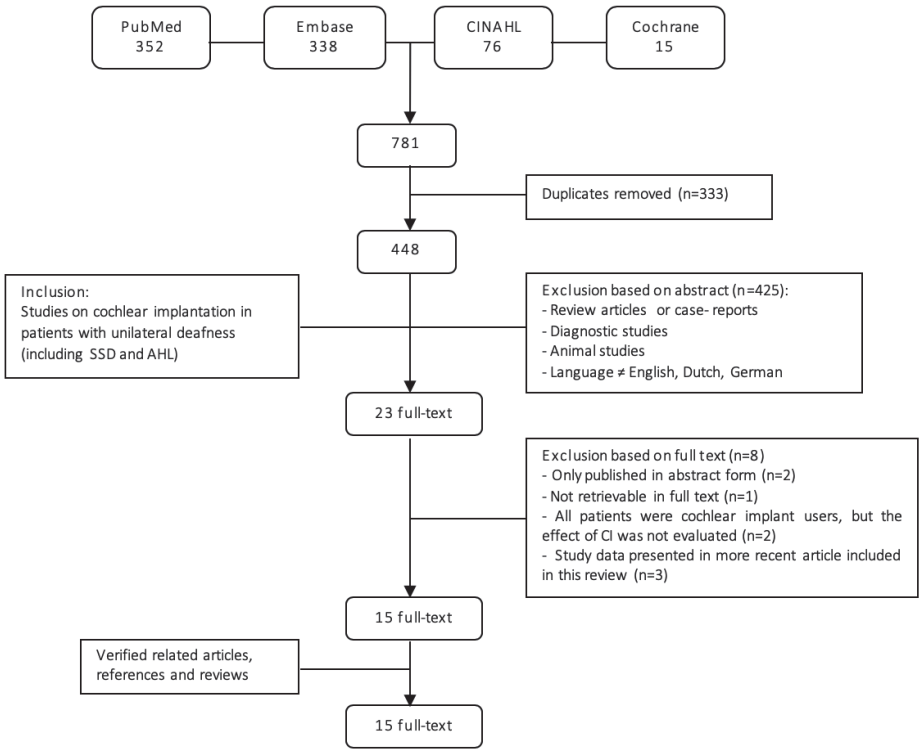
Study selection

A.v.Z. and J.P.M.P. screened titles and abstracts of the retrieved records and subsequently the full- text versions of the potentially relevant articles which evaluated the effect of CI in patients with unilateral hearing loss . Criteria for inclusion and exclusion are shown in Figure 1. Although we aim to focus on the effect of CI for patients with SSD, we also included studies in which patients with AHL were investigated. This was done, because there is no international consensus on the definitions for SSD and AHL.

In this study, we define SSD as a SNHL with a threshold of ≥70dB HL in the affected ear and a threshold of ≤30 dB HL in the better ear. AHL is defined as a SNHL with a threshold of ≥70dB HL in the affected ear and a threshold of <70 dB HL in the better ear.

We assessed the eligibility of the trials independently and settled any differences in opinion by discussion. The outcomes of interest were: speech perception in noise, sound localization, quality of life (QoL) and tinnitus.

Figure 1. Study selection process.



Abbreviations: CI, cochlear implantation; SSD, single-sided deafness; AHL, asymmetrical hearing loss.

Assessing quality of studies

Predefined criteria were used for assessment of the directness of evidence and risk of bias of the selected studies (see Table 2). Discrepancies were discussed until consensus was reached. All studies with a sample size of less than 5 patients or with either a low directness of evidence or a high risk of bias were excluded for further review.

Studies were classified as having high directness of evidence if they complied with all four criteria, as moderate directness of evidence if they complied with three criteria and as low directness of evidence if they complied with only one or two criteria. If studies complied with all five or four criteria used to assess risk of bias, they were classified as having a low risk of bias, with three as a moderate risk of bias and with one or two as a high risk of bias.

Data extraction

Study characteristics and outcome data of the included studies were extracted by the first two authors, disagreements were resolved by discussion. Study characteristics are presented in Table 3.

RESULTS

Search strategy and study selection

The search in the PubMed, Embase, Cochrane Library and CINAHL databases retrieved a total of 781 articles. Figure 1 shows how the search results were further assessed. After removal of duplicates and selecting articles by title or abstract, 23 articles were left to read in full-text.

Eight more studies could be discarded following full-text assessment. Three studies presented study data which were also presented in more recent articles included in this review,[13-15] in two studies all patients were cochlear implant users, but the effect of CI was not evaluated,[16,17] two studies were only published in abstract[18,19] and one study could not be retrieved in full-text.[20] Cross-reference checking and related article search yielded one additional article, however, this study was excluded because it was only published in abstract form.[21] Fifteen studies, including a total of 166 patients, were eligible for critical appraisal.

Assessing quality of studies

The critical appraisal of the 15 studies is presented in Table 2. All studies evaluated the effect of CI on at least one of our outcomes of interest. Three studies reported on less than five patients.[22-24] We therefore excluded these studies for further review. Important limitations in the directness of evidence were found in two studies and therefore we did not further review these studies.[25,26] Both studies scored low on patient population, they assessed only one of our outcomes of interest and there was no follow-up moment at either

Table 2. Assessment of quality of studies

			Directness of evidence (DoE)								Risk of bias (RoB)					
					Outcome			FU								
	Study design	Sample size (*n*)	Patients	Treatment	Binaural hearing	Tinnitus	Quality of Life	6 months	12 months	DoE (total)	Treatment allocation	Blinding	Standardization (T)	Standardization (O)	Complete data	RoB (total)
Arndt 2010	PCS	11	●	●	●	●	●	●	○	H	○	○	●	●	●	M
Buechner 2010	PCS	5	?	●	●	●	○	●	●	M	○	○	●	●	●	M
Cadieux 2013	PCS	5	○	●	●	○	○	○	○	L	○	○	●	●	○	H
Firszt 2012	PCS	10	○	●	●	○	●	●	○	M	○	○	●	●	●	M
Hansen 2013	PCS	29	○	●	●	○	○	●	●	M	○	○	●	●	○	H
Hassepass 2013[a]	PCS	3	●	●	●	○	●	●	●	H	○	○	●	●	○	H
Hassepass 2013[b]	PCS	3	●	●	●	●	●	●	●	H	○	○	●	●	●	M
Jacob 2011	RCS	13	●	●	○	●	○	○	○	M	○	○	●	●	●	M
Kleine Punte 2012	PCS	7	?	●	○	●	○	●	○	M	○	○	●	●	●	M
Mertens 2012	PCS	15	○	●	○	●	○	○	●	M	○	○	●	●	●	M
Ramos 2011	PCS	10	○	●	●	○	●	○	○	L	○	○	●	●	●	M
Stelzig 2011	RCS	4	●	●	●	○	●	○	○	M	○	○	●	●	●	M
Távora-Vieira 2012	PCS	9	●	●	○	●	○	○	○	M	○	○	●	●	●	M
Van de Heyning 2008	PCS	22	○	●	○	●	○	●	●	M	○	○	●	●	●	M
Vermeire 2009	PCS	20	○	●	●	○	●	○	●	M	○	○	●	●	●	M

Directness of evidence

Patients: ● = patients with SSD; defined as a sensorineural hearing loss with a threshold of ≥70dB HL in the affected ear and a threshold of ≤30 dB HL in the better ear; ○ = other

Treatment: ● cochlear implantation; ○ = other

Outcome 1: ● = binaural hearing tests; ○ = no information about binaural hearing provided

Outcome 2: ● = tinnitus; ○ = no information about tinnitus provided

Outcome 3: ● = quality of life; ○ = no information about quality of life provided

Follow-up (FU)1: ● = ≥ 6 months; ○ = ≤ 6 months

Follow-up (FU)2: ● = ≥ 1 year; ○ = ≤ 1 months

Risk of bias

Treatment allocation: ● = randomized or concealed; ○ = neither randomization nor concealment; ? = unclear, no information provided

Blinding of intervention and interpretation of outcomes: ● = patients and personnel blinded; ○ = only patients blinded or no blinding; ? = unclear, no information provided

Standardization (T) of cochlear implantation (implant type and processor mentioned): ○ = yes; ● = no; ? = unclear, no information provided

Standardization (O) of outcome measure: ● = yes; ○ = no; ? = unclear, no information provided

Completeness of outcome data for primary outcome: ● = below 15% missing data; ○ = 15% or more missing data; ? = unclear, no information provided

Study Design

RCS = retrospective case series; PCS = prospective case series

Table 3. Study characteristics

Study	N	Age Yr, Mean, (SD), [range]	DoD Mo, Mean, (SD) [range]	CoD	Implant indication	Implant type	Pure Tone Audiometry (0.5, 1, 2, 4 kHz) Mean, (SD), [range]	Outcome measures	FU duration
Arndt 2010	11	43.6* (11.9*) [23.0-68.0]	25.0* (31.3) [4.0-110.0]	SSD	HL	Nucleus3	Non-implanted ear: 98.4 dB HL*(12.5*) [80.0-117.0dB] Implanted ear: 12.9 dB HL* (6.9*) [7.0-30.0dB]	Speech perception in noise: HSM, OlSa Sound localization Tinnitus: VAS-distress QoL: SSQ, HUI3	6 mo
Buechner 2010	5	50.0* (5.2*) [42.2-56.0]	33* (17.8*) [18.0-62.0]	?	Tinnitus	HiRes	-	Speech perception in noise: OlSa Tinnitus: VAS-loudness and distress	1, 3, 6 and 12 mo
Firszt 2012	10	53.0 (24.4) [26.0-82.0]	206.0 (168.6) [12.0-480.0]	AHL	HL	Nucleus	Non-implanted ear: 56.0 dB HL (21.7) [27.0-88.0] Implanted ear: 101.0 dB HL (16.1) [72.0-120.0]	Speech perception in noise: CNC, HINT, TIMIT Sound localization QoL: SSQ	Postlingual deaf: 6 mo Prelingual deaf: 12 mo
Jacob 2011	13	43.3* (13.6*) [25-63]	65* (90.2*) [4.0-324.0]	SSD	HL	Nucleus / Med-El	Non-implanted ear: <30.0 dB HL Implanted ear: >80.0 dB HL	Speech perception in noise: Freiburg monosyllable test, HSM, OlSa Sound localization	Different per patient
Kleine Punte 2013	7	-	54.4* (36.5*) [9.0-108.0]	?	Tinnitus	Med-El	-	Tinnitus: VAS-loudness, TQ	1, 3 and 6 mo

Mertens 2013	15	51.0* (11.2*) [22.0-63.0]	-	?	Tinnitus	Med-El	-	Tinnitus: VAS-loudness, TQ	Different per patient and outcome TQ: 12 and 36 mo
Távora-Vieira 2013	9	57.0* (7.9*) [45.0-70.0]	188.0*(214.1*) [7.0-480.0]	SSD	HL	Med-El	Non-implanted ear: 16.2 dB HL* (7.6*) [3.0-28.0] Implanted ear: 92.1 dB HL* (15.2*) [74.0-110.0]	Speech perception in noise: BKB QoL: SSQ Tinnitus: TRQ	3 mo
Vd Heyning 2008	22	51.1 (12.4) [22.9-71.6]	105.0(134.9) [18.0-606.0]	AHL	Tinnitus	Med-El	Non-implanted ear: 41.0dB HL (24) [10.0-70.0] Implanted ear: 112 dB HL (19.8)	Tinnitus: VAS-loudness, TQ	1, 3, 6, 12, 18 and 24 mo
Vermeire 2009	20	51.6 (12.5) [22.9-71.6]	111.0(139.9) [18.0-606.0]	AHL	Tinnitus	Med-El	Non-implanted ear: 36.9dB HL* (24.6*) [10.0-79.0] Implanted ear: ?	Speech perception in noise: LIST QoL: SSQ	12 mo

** Derived from tables/graphs or self-calculated.*

Abbreviations: N, number of patients included in study; yr, year; mo, months; SD, standard deviation; DoD, duration of deafness; CoD, classification of deafness; FU, follow-up, SSD, single-sided deafness, AHL, asymmetric hearing loss, HL, hearing loss; HSM, Hochmair-Schulz-Moser sentence test; OISa, Oldenburger sentence test; QoL, Quality of Life; SSQ, Speech, Spatial and Qualities of Hearing Scale; HUI3, Health Utilities Index 3; IOI-HA, Outcome Inventory for Hearing Aids questionnaires; VAS, Visual Analogue Scale; TQ, Tinnitus Questionnaire, THI, Tinnitus handicap inventory, BKB, Bamford-Kowal-Bench, TRQ, tinnitus reaction questionnaire, LIST, Leuven Intelligibility Sentence Test.

6 or 12 months. Because none of the included studies was conducted as a randomized controlled trial (RCT) and none of the studies evaluated a control group, a low risk of bias was not assessed in one of the included articles. Blinding did not take place in any of the studies because both professionals and patients are aware of CI. Based on our criteria, three studies were considered as having a high risk of bias due to incomplete data and were excluded for further analysis.[23,25,27] After the quality assessment, nine studies (n = 112 patients) were left for further data extraction and analysis.

Data extraction

There is a large degree of clinical heterogeneity amongst the studies in terms of participants (classification of hearing loss [SSD vs. AHL], duration of deafness and the indication for CI [hearing loss vs. tinnitus]), test conditions (implant-on vs. implant-off and pre-implant vs. post-implant), follow-up duration and outcome measurements (i.e., different test configurations, word tests and/or questionnaires) (Table 3). Owing to this heterogeneity, pooling of data was not possible. We therefore summarized the extracted data of the different outcomes (Tables 4 - 7). When studies did not report mean data or standard deviations in their text or tables, we did not derive them from graphs. Furthermore, in Tables 4 – 7 several *p*-values are missing because they were not reported.

Speech perception in noise

Six studies reported on speech perception in noise (n = 68) ([28-33]). In Table 4 the extracted data are summarized. Mertens et al. investigated the effect of a cochlear implant on tinnitus reduction ipsilaterally and improved speech perception in noise contralaterally and therefore their results are not taken into account in this section.[34]

Speech perception in noise can be measured using different configurations of spatially separated loudspeakers. We will indicate the configurations by abbreviating sound (S) and noise (N) followed by the direction; 'ci' for sound or noise coming from the CI side, 'be' for the 'better ear' side and finally '0' for 0 degrees azimuth.

Speech perception in noise was evaluated by five studies in terms of the signal-to-noise ratio (dB), at which 50% of sentences is understood correctly.[28,30-33] Both Arndt et al. and Távora-Vieira et al. demonstrated that sound perception in noise improved most in the SciNbe configuration.[28,31] Also Vermeire et

al. found a positive effect of cochlear implant activation, but significance of the results differs per subgroup; both the contralateral hearing aid (HA) and normal hearing (NH) subgroups gain significant benefit from the CI in the SciN0 configuration, but only the HA subgroup also experiences significant benefit in the S0Nci configuration.[32] In agreement with Arndt et al., they did not find significant differences in the S0N0 configuration. Jacob et al. did not find any changes in signal-to-noise ratios between the CI-on and CI-off conditions.[30] Finally, Buechner et al. did not provide any numerical data, but state that 3 out of 5 patients experienced a significant improvement in speech perception in noise.[33]

Three studies evaluated speech perception in noise as the total percentage of correctly repeated words.[28-30] Arndt et al. found statistically significant improvement in the SciNbe configuration for the cochlear implant group compared to the other conditions, equivalent to their findings with the OlSa test.[28] Interestingly, cochlear implant performance in the SbeNci configuration was superior to the scores in the CROS and BCD conditions, but not significantly different from the unaided group scores. For the prelingual onset of deafness group in the study of Firszt et al., no significant improvement was found between the HA alone condition and the bimodal condition (cochlear implant + HA).[29] For the postlingual deaf patients, there is an improvement after CI, but they did not report significance on group level. The speech perception in noise scores in the study of Jacob et al. was not significantly different between the CI-on and CI-off conditions.[30]

Table 4. Speech perception in noise

Study	Subgroups	Configuration*	Pre-implant			Post-implant		Statistics	FU duration
			Unaided	BCD	CROS	CI-on	CI-off		
Arndt 2010**	-	HSM (%)							6 mo
		S0N0	74.1	-	-	76.4	-	ns	
			-	74.1	-			ns	
			-	-	76.9			ns	
		SciNbe	14.6	-	-	42.5	-	$p < 0.01$	
			-	10.4	-			$p < 0.01$	
			-	-	24.5			$p = 0.03$	
		SbeNci	99.5	-	-	100.0	-	ns	
			-	98.6	-			$p = 0.02$	
			-	-	98.6			$p = 0.03$	
		OlSa (dB)							
		S0N0	***	-	-	***	-	-	
		SciNbe	-0.6			-6.2		$p < 0.01$	
		SbeNci	-14.1			-14.6		ns	
Firszt 2012	Prelingual	CNC + HINT + TIMIT (%)							12 mo
		S0N0	No quantitative data; only graph presented (per patient). No significant improvement between the bimodal compared to the HA-alone (better ear) or pre-implant condition.						
	Postlingual	CNC (%)							6 mo
		S0N0	6			50	-	-	
		HINT (%)							
		S0N0	10			57	-	-	
		TIMIT (%)							
		S0N0	1			25	-	-	
Jacob 2011	-	OlSa (dB)							6 – 48 mo
		SciN0	-	-	-	-4.5	-4.5	-	
		S0N0				-9.0	-9.0	-	
		SbeN0				-9.0	-9.0	-	

		HSM / Freiburg monosyllable test (%) No quantitative data; only graphs presented. The speech perception scores were not statistically different in the CI-on condition compared to the CI-off condition.						
Távora-Vieira 2013	-	BKB, in dB (SD)						3 mo
		S0N0	6.0 (4.0)			3.0 (3.0)	-	-
		S0Nci	-3.0 (2.0)			-3.0 (2.0)	-	-
		S0Nbe	1.0 (3.0)			-2.0 (2.0)	-	-
		SciNbe	2.0 (2.0)			-3.0 (2.0)	-	-
Vermeire 2009	HA	LIST, in dB (SD)						12 mo
		S0N0	-	-	-	4.1 (4.6)	7.4 (9.2)	ns
		S0Nci				0.3 (4.4)	4.1 (7.0)	$p = 0.03$
		SciN0				3.5 (6.4)	10.0 (9.8)	$p = 0.04$
	NH	S0N0	-	-	-	-3.0 (2.7)	-2.7 (3.0)	ns
		S0Nci				-5.5 (5.5)	-6.7 (4.3)	ns
		SciN0				-1.5 (2.8)	0.2 (2.8)	$p < 0.01$
Buechner 2010	-	OlSa (dB)						Unclear
		S0Nbe	For 3 out of 5 of the participants the CI led to a highly significant improvement ($p < 0.01$)					

** Test set-up: S = sound, 0 = 0 degrees azimuth, N = noise, CI = cochlear Implant side, be = better ear*
*** Arndt investigated in a test setting with loud speakers at ±45 degrees azimuth, all other studies examined in ±90 degrees configurations.*
**** No numerical data provided. The authors state that there is no difference (0.0 dB) between the unaided and CI-on condition for S0N0 configuration.*
Abbreviations: FU: follow up, BCD: Bone Conduction Device, CROS: Contralateral Routing Of Signal, CI: cochlear implant, HSM: Hochmair-Schulz-Moser test, mo: months, ns: not significant, OlSa: Oldenburg Satz test, CNC: consonant-vowel nucleus-consonant test, HINT: hearing in noise test, BKB: Bamford-Kowal-Bench speech recognition in noise test, HA: contralateral hearing aid group, NH: normal hearing group, LIST: Leuven Intelligibility Speech Test.

Sound localization

Three studies (n = 34) reported on sound localization.[28-30] Data of the individual studies are presented in Table 5. Although the three studies used different test set-ups, they all used the localization error as outcome measure to assess localization. The localization error is the mean difference in degrees between the location of the sound source and the source indicated by the patient.

Arndt et al. found that the localization error reduced significantly after CI compared to the pre-implant condition with either a CROS or BCD or the unaided condition.[28] In the study of Jacob et al., participants were tested at different time points after CI. They reported a reduction of the localization error from 48.0° tot 4.0° in the CI-on condition compared to the CI-off condition. However, no statistics were presented.[30] Firszt et al. analyzed the data of postlingual deaf patients separately from patients with prelingual onset of deafness.[29] They showed that the localization error reduced significantly in the bimodal (cochlear implant + HA) post-implant condition compared to hearing with the HA-alone (in better ear) in the postlingual deaf patients. This improvement was not found in the prelingual deaf patients.

Quality of life

QoL was reported in four studies (n = 50).[28,29,31,32] Data of the individual studies are presented in Table 6. All studies used the Speech, Spatial and Qualities of hearing (SSQ) questionnaire to assess QoL. The SSQ is divided into three subsections: 1) Speech, 2) Spatial and 3) Quality of hearing.

In the study of Arndt et al. patients scored better on all sections of the SSQ in the condition with their cochlear implant compared to the three pre-implant conditions (unaided, BCD or CROS).[28] The scores were significantly higher in the Speech and Spatial subsections. No significant differences were found in the Quality of hearing subsection. Vermeire et al. showed a significant improvement after CI compared to the pre-implant monaural condition in both the HA and NH group in the Speech and Quality of hearing subsections and in the NH group also in the Spatial subsection.[32] In the study of Távora-Vieira, a significant improvement on all three subsections of the SSQ was demonstrated after CI compared to the pre-implant condition.[31] Firszt et al. showed a significant improvement pre- to post-implantation for the Speech and Spatial subsections in the postlingual deaf patients after 6 months and for the prelingual deaf patients only for the Spatial subsection after 12 months.[29]

No significant improvements were observed in the Quality of hearing subsection.

One study evaluated QoL by means of the Health Utilities Index 3 (HUI3).[28] They reported a significantly increased overall group score in the cochlear implant group compared to the pre-implant condition with either CROS or BCD. No significant improvement was found compared to the unaided condition.

Table 5. Sound localization

Study	Test setup	Subgroup	Pre-implant			Post-implant		Statistics	FU duration
			Unaided	BCD	CROS	CI-on	CI-off		
Arndt 2010	7 loudspeakers in a 180° arch with intervals of 30°. *Stimulus:* OlSa sentences (mean 65 dB)	-	33.9°	-	-	15.0°	-	$p < 0.01$	6 mo
			-	30.4°	-			$p < 0.01$	
			-	-	39.9°			$p < 0.01$	
Jacob 2011	11 loudspeakers in 180° arch with intervals of 18°. *Stimulus:* noise at different loudness (60dB, 70dB and 80dB)	-	-			4.0°	48.0°	-	6 – 48 mo (differs per patient)
Firszt 2012	15 loudspeakers in 140° arch with intervals of 10° *Stimulus:* monosyllabic words (mean 60 dB)	Prelingual	No quantitative data; only graph (per patient) presented. No significant improvement reported after implantation in the bimodal compared to the HA-alone (better ear) condition.					-	6 mo
		Postlingual	No quantitative data; only graph presented. The localization error after implantation significantly reduced in the bimodal compared to the HA-alone (better ear) condition.					$p \leq 0.05$ (for all patients)	6 mo

Abbreviations: FU, follow up; BCD, Bone Conduction Device; CROS, Contralateral Routing Of Signal; CI, cochlear implant; mo, months; HA, hearing aid.

Table 6. Quality of Life.

Study	Subgroups	Test	Subsection	Pre-implant (SD)			Post-implant (SD)	Statistics	FU
				Unaided	BCD	CROS	CI		
Arndt 2010	-	SSQ	Speech	2.6	-	-	5.8	$p = 0.01$	6 mo
				-	2.9	-		$p < 0.01$	
				-	-	3.1		$p = 0.01$	
			Spatial	2.3	-	-	5.7	$p < 0.01$	
				-	2.4	-		$p < 0.01$	
				-	-	2.6		$p = 0.03$	
			Quality	5.9	-	-	7.8	ns	
				-	5.3	-		ns	
				-	-	5.5		ns	
		HUI3	Overall	0.6	-	-	0.8	ns	
				-	0.7	-		$p < 0.01$	
				-	-	0.7		$p < 0.01$	
Vermeire 2009	HA	SSQ (SD)	Speech	2.1 (1.2)			4.3 (1.5)	$p = 0.01$	12 mo
			Spatial	1.9 (1.0)			2.6 (1.6)	ns	
			Quality	3.5 (1.7)			5.8 (2.2)	$p < 0.01$	
	NH	SSQ (SD)	Speech	3.9 (1.4)			6.0 (1.4)	$p < 0.01$	
			Spatial	3.0 (1.5)			5.3 (1.7)	$p < 0.01$	
			Quality	5.8 (1.5)			6.9 (1.6)	$p = 0.05$	
Távora-Vieira 2013	-	SSQ	Speech	No quantitative data, only graph presented. They reported a significant improvement for all three subsections.				$p < 0.01$	3 mo
			Spatial					$p < 0.01$	
			Quality					$p < 0.01$	
Firszt 2012	Prelingual	SSQ	No quantitative data, only graph presented (per patient). Significant benefit from pre- to post-implant on the Spatial subsection.					-	12 mo
	Postlingual	SSQ	No quantitative data, only graph presented. Significant benefit from pre- to post-implant on the Speech and Spatial subsections.					-	6 mo

Abbreviations: SD, standard deviation; FU, follow up; BCD, Bone Conduction Device; CROS, Contralateral Routing Of Signal; CI, cochlear implant; mo, months; ns, not significant; NH, normal hearing group; HA, contralateral hearing aid group; SSQ, Speech, Spatial and Qualities of Hearing questionnaire; HUI3: Health Utilities Index 3.

Tinnitus

Tinnitus was reported in six studies (n = 69).[10,28,31,33-35] Data of the individual studies are presented in Table 7. Several subjective scales were used to assess either tinnitus distress or tinnitus loudness and the included studies reported tinnitus at different time points after CI.

Five studies used a Visual Analog Scale (VAS) to assess tinnitus.[10,28,31,34,35] Three of them reported a significant reduction of the tinnitus distress or loudness after CI.[10,28,34] The remaining studies also showed a reduction of tinnitus, but they did not present statistics.[33,35] Furthermore, two studies showed that the tinnitus reoccurred after switching off the implant.[28,35]

Three studies used the Tinnitus Questionnaire (TQ) to evaluate the effect of CI on tinnitus.[10,34,35] Two of them reported a significant reduction of tinnitus,[10,35] Mertens et al. did not note significance.[34]

Only one study used the Tinnitus Reaction Questionnaire (TRQ) to assess tinnitus distress.[31] They reported a reduction of tinnitus varying from 77% to 100%, but again, no statistics were presented.

Table 7. Tinnitus

Study	Test	Pre-implant (SD)	Post-implant (SD)		Statistics	FU duration
			Implant-on	Implant-off		
Arndt 2010	VAS distress	5.0	0.0	-	$p < 0.01$	6 mo
			-	5.0		
Kleine Punt 2013	VAS loudness*					6 mo
	(SD)	8.3 (1.1)	2.8 (1.7)	8.0 (1.2)	-	
	TQ (SD)	60.0 (15.6)	39.4 (12.4)	-	$p = 0.04$	
Mertens 2013	VAS loudness					
	(SD)	-	3.4 (2.5)	7.2 (2.6)	$p < 0.01$	12 mo
	TQ (SD)	58.1 (13.7)	32.8 (19.3)	-	-	12 mo
			26.3 (20.0)	-	-	36 mo
Vd Heyning 2008	VAS loudness	8.5 (1.3)	3.5 (2.5)	-	$p < 0.01$	1 mo
	(SD)		-	7.0 (2.8)	$p < 0.01$	
			2.2 (2.0)	6.6 (3.0)	-	3 mo
			2.3 (1.5)	6.3 (2.8)	-	6 mo
			2.4 (1.8)	6.6 (2.6)	-	12 mo
			2.7 (2.0)	6.4 (3.1)	-	18 mo
			2.5 (1.9)	6.1 (2.9)	-	24 mo
	TQ (SD)	58.4 (13.9)	33.3 (16.6)	-	$p < 0.01$	1 mo
			32.4 (19.9)	-	-	3 mo
			33.8 (21.0)	-	-	6 mo
			34.3 (20.1)	-	-	12 mo
			31.4 (18.8)	-	-	18 mo
			38.9 (19.4)	-	-	24 mo
Távora-Vieira 2013	TRQ distress	Significant decrease in TRQ score (range 77.0-100.0%).			-	3 mo
Buechner 2010	VAS distress and loudness combined	Significant long-term decrease in VAS score (3/5 patients, 60%)) and a significant decrease in VAS score in certain situations (2/5 patients, 40%)).			-	Unclear

Abbreviations: SD, standard deviation; FU, follow-up; mo, months; VAS, Visual Analogue Scale; TQ, tinnitus questionnaire; TRQ, Tinnitus Reaction Questionnaire.

** Discrepancy between results mentioned in the text and the tables. We adopted the results from the table.*

DISCUSSION

The major strength of this study is that we reviewed the effects of CI on multiple clinical outcomes in patients with unilateral deafness systematically. To date, only non-systematic reviews have been conducted on this topic.[36-38] Our systematic review is characterized by a transparent search strategy (Table 1), study selection and critical appraisal of selected studies. Also, we had strict criteria for including studies in our final data extraction, yielding better quality evidence. In addition to other reviews that only summarized data, we showed the results of individual studies in comprehensive tables per outcome.

One of the most important findings of this systematic review is that there are only non-randomized, low or moderate level of evidence studies on the topic of CI for SSD. This needs to be taken into consideration when interpreting the described results.

Current review showed varying results for speech perception in noise after CI compared to other modalities in patients with unilateral deafness. Although the success rates differed and the quality of the studies was suboptimal, modest improvements were observed. The largest significant improvement was reported when sound was presented to the cochlear implant side.[28-32] All three studies that reported on sound localization showed a substantial improvement after CI.[28-30] Also QoL improved substantially after CI when assessed with the SSQ, where most benefit was observed on the Speech subsection.[28,29,31,32] Our results on the previously described outcomes are generally congruent with the results of Kamal et al. and Vlastarakos et al.[36,37]

Historically, the initial intention of CI in unilateral deaf patients was not the restoration of binaural hearing, but the treatment of tinnitus. All studies that focused on tinnitus in current review objectified a substantial suppression of the complaints based on both the VAS and the TQ scores[10,28,33-35] as by the TRQ scores.[31] None of the included studies reported tinnitus worsening after CI. These results indicate that there is a positive effect of CI on both tinnitus distress and loudness. Furthermore, we reported that two included studies showed that the tinnitus reoccurred after switching off the cochlear implant.[28,35] This finding supports the paradigm that tinnitus results from cochlear deafferentiation.[10] In 2012, Arts et al. reviewed the literature on CI in patients with SSD to investigate the effect on tinnitus suppression.[38] The results of their review and the review by Vlastarakos et al. are congruent with our results.[37]

Besides the lack of high-quality evidence, there are some other limitations that we have to discuss. First, the sample sizes of the included studies are small. Two studies performed subgroup analysis which will eliminate statistical power when subgroups are already small.[29,32]

Next, there is a large degree of clinical heterogeneity amongst the studies that were included, which made it impossible to pool data. We will now summarize the most important differences in study characteristics: 1) The classification of deafness varies between and within study populations.[10,29,32] The hearing thresholds for SSD and AHL are different, and therefore the affected contralateral ear in patients with AHL may have a negative impact on the hearing outcomes after CI compared to patients with SSD; 2) There is a large variation in the duration of deafness, again both between and within study populations. From studies in bilaterally deaf patients, it is known that, amongst other factors, the shorter the duration of deafness is, the better the cochlear implant performance.[39,40] In five of the studies that were included in this review the duration of deafness even surpassed 10 years;[10,29-32] 3) the indication for CI differs amongst studies; 4) the onset of deafness varies within and between studies or is not mentioned. Only Firszt et al. presented their results for patients with prelingual onset and postlingual deafness separately.[29] They did not show a benefit from CI in patients with prelingual onset of deafness when sound localization and speech perception in noise were concerned. This finding highlights the possible limitation of CI in prelingual deaf patients. However, Firszt et al. reported on only three patients with prelingual onset of deafness; 5) The follow-up time differed amongst and within studies, impeding comparison between studies. This may have influenced the results, since we know that the duration of cochlear implant use is an important predictor of speech perception;[40] and 6) Studies used different tests to assess their outcomes and different test conditions were used to examine the differences between monaural and binaural hearing. This counts most for speech perception in noise and may have led to the varying results for this outcome. In several studies, patients were asked to turn off their cochlear implant. The unilateral listening condition created in this manner cannot be compared to the pre-implant condition.

Finally, there are no paediatric studies that passed our critical appraisal. Therefore no conclusions can be drawn about the effectiveness of CI in children with unilateral hearing loss. Children with unilateral deafness are at increased risk of academic difficulties and behavioural issues.[41] High-quality research for this specific group should be conducted.

CONCLUSION

In conclusion, this systematic review shows that there are no high level-of-evidence studies concerning CI in patients with SSD or AHL. Current literature suggests important benefits of CI in this population regarding sound localization, QoL and tinnitus. Although results for speech perception in noise are promising as well, varying results between studies were reported for this outcome. This is possibly caused by the large clinical heterogeneity. Given the limited but promising results of CI for patients with SSD or AHL, larger and high-quality studies are certainly warranted before CI can be considered as standard care.

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CHAPTER

9

Summarizing discussion

In **chapter 1** (general introduction) we describe the anatomy of the human ear, the physiology of normal hearing and the pathophysiology of hearing loss. Subsequently cochlear implantation (CI) and its selection criteria are discussed. Unilateral cochlear implantation (UCI) has become the standard of care for adult patients with bilateral severe to profound sensorineural hearing loss (SNHL). We present an overview of the advantages of binaural hearing based on three principles; the head shadow effect, the binaural summation effect and the squelch effect. Due to this knowledge, interest in bilateral cochlear implantation (BiCI) is growing. Although benefits of BiCI compared to UCI have been reported, Dutch insurance companies reimburse only one cochlear implant in adults, based on a perceived lack of high-quality studies supporting BICI. Therefore, our study group started a randomized controlled trial (RCT) in which we compared simultaneous BiCI to either UCI or sequential BiCI in postlingually deafened adults. The patients in the sequential group first received one cochlear implant and after 2 years they received their second implant. ***Part one*** of this thesis focusses on some of the results of this RCT. In ***part two*** we focus on future indications for CI. Selection criteria for CI have broadened during the last years and it is expected that a cochlear implant will also be provided for new indications in the near future. We explain that tinnitus is a disturbing symptom in patients with severe to profound SNHL and that current literature in general reports a reduction of tinnitus after CI in these patients. At last, we give information about single-sided deafness (SSD) and describe the reported benefits of CI in this patient group.

PART ONE – BILATERAL COCHLEAR IMPLANTATION

1.1. Main results and conclusions per chapter – Bilateral cochlear implantation

Chapter 2 presents the first results of the RCT comparing simultaneous BiCI to UCI in postlingually deafened adults at 1-year follow-up. Thirty-eight patients were included in this study and randomly allocated to either simultaneous BiCI or UCI. The primary outcome was speech intelligibility in noise, with speech and noise coming from straight ahead (Utrecht-Sentence Test with Adaptive Randomized Roving levels (U-STARR)). Secondary outcomes were speech intelligibility in noise with spatially separated sources (SISSS), speech intelligibility in silence (Dutch consonant-nucleus-consonant (CNC) test), localization capabilities and

self-reported benefits assessed with different quality of hearing questionnaires. After 1 year of follow-up, there were no significant differences between groups on the U-STARR or CNC test. The BiCI group performed significantly better than the UCI group on the SISSS. Furthermore, patients in the BiCI group were better able to localize sounds. These results were consistent with patients' self-reported hearing capabilities. This chapter shows that there is a significant benefit of simultaneous BiCI compared to UCI in postlingually deafened adults.

In **chapter 3** we present the results of the RCT at 2-year follow-up. Again, the simultaneous BiCI group performed significantly better than the UCI group on the SISSS and also the localization capabilities were significantly better in this group. Comparable results were found for both groups on the U-STARR and CNC test. The results were consistent with patients' self-reported hearing capabilities. Because we did not find significant differences between groups on the QoL surveys, the suitability of these instruments for evaluation of cochlear implant-treatment is doubtful. This chapter demonstrates important benefits of simultaneous BiCI compared to UCI that remain stable over the second year of implant use. Furthermore, by using a within subject design, we compared the 1-year follow-up data of chapter 2 with the 2-year follow-up data of this chapter; no significant differences were found for any of the objective and subjective outcomes.

Chapter 4 evaluates the occurrence of a squelch effect in the first 3 years after simultaneous BiCI. A prospective study as part of the RCT comparing simultaneous BiCI to UCI or sequential BiCI was performed. In the simultaneous BiCI group, the squelch effect was measured yearly with the SISSS. Bilateral results were compared to unilateral results by switching off the implant at the noise side. The squelch effect was investigated for patients' best performing ear and for the left and right ears separately. We found a measurable benefit from the squelch effect in the simultaneous BiCI group after 2 years in their best performing ear and after 3 years in both ears. This effect size increased over time. These observations suggest that the brain uses interaural differences to segregate speech from noise after simultaneous BiCI. The growth of the squelch effect over time suggests continued development of cortical integration and differentiation of inputs beyond the first years after implantation.

In **chapter 5** we investigate whether simulated unilateral hearing (switching off one cochlear implant) results in the same outcomes as real-life unilateral

hearing with one cochlear implant and a non-implanted contralateral ear. In previous studies the unilateral hearing situation is often simulated by switching off one of the implants in bilateral implant users. This chapter assesses the accuracy of this test method by using the outcomes of one arm (sequential BiCI group) of the RCT mentioned in the earlier chapters. The primary outcome was speech perception in noise from straight ahead. Secondary outcomes were speech perception in silence, speech intelligibility in noise from spatially separated sources and localization capabilities. A within-subject design was used to compare the results of hearing with one implant and a non-implanted contralateral ear (1-year and 2-year follow-up) to the results of switching off one implant after sequential BiCI (3-year follow-up). No significant differences on any of the outcomes after 1-year, 2-year or 3-year follow-up were found. In this chapter we show that simulating unilateral hearing by switching off one implant is a reliable method to compare unilateral and bilateral hearing in bilaterally implanted patients.

1.2. Comparison to and critical review of the literature – Bilateral cochlear implantation

1.2.1. Simultaneous bilateral cochlear implantation

Our RCT shows that there is a significant benefit of simultaneous BiCI compared to UCI in difficult everyday listening situations in which speech and noise come from different directions. Furthermore, bilaterally implanted patients are able to localize sound, which was impossible for unilaterally implanted patients. We demonstrated these benefits after a 1-year (**chapter 2**) and 2-year (**chapter 3**) follow-up, so the reported benefits of simultaneous BiCI remained stable over the second year of implant use.

As in our study, prior studies found no benefit of BiCI compared to UCI for the primary outcome measure of our RCT, speech intelligibility-in-noise with speech and noise coming from straight ahead.[1-4] However, the benefit of BiCI compared to UCI in more difficult listening situations in which speech and noise come from different directions was also reported in cohort studies by researchers in the past.[1,3,4,5] Corresponding to our results, several earlier studies already showed that the addition of a second implant makes is possible for cochlear implant users to localize sounds.[3,6-9]

1.2.2. Actual versus simulated unilateral hearing

Previous studies concerning BiCI versus UCI are mostly non-randomized cohort studies and often bilaterally implanted patients were asked to switch off one implant to assess differences between the monaural and binaural situation.[1,2,4,5,7,9-13] Our hypothesis was that this simulated unilateral listening situation would not be representative for an actual UCI situation. The electrode would have damaged the cochlea and thus diminished any residual hearing. On the other hand, bilateral implant users are trained to listening with two ears in everyday life, while unilateral implant users may not have used the contralateral ear for an extensive period of time. The design of our RCT gave us the unique opportunity to assess the accuracy of this test method by evaluating the data of the sequential BiCI group before and after the second implantation in **chapter 5**. No significant differences were found for any of the objective outcomes and therefore simulating unilateral hearing by switching off one cochlear implant seems a reliable method to compare unilateral and bilateral hearing in bilaterally implanted patients.

1.2.3. The squelch effect

The existing literature proves that the difficulties unilateral cochlear implant users experience with speech intelligibility in noise are partially overcome in bilaterally cochlear implant users due to the advantages of binaural hearing. As explained previously, binaural hearing benefits are quantified with the head shadow effect, the summation effect and the squelch effect. The most robust binaural effects in bilateral cochlear implant users are reported for the head shadow effect ranging from 4 to 7dB, followed by the binaural summation effect with moderate benefits ranging from 1.5 to 2.9 dB. Both benefits appear early in the follow-up period and remained constant through 4 years of follow-up. Limited evidence was available for the squelch effect in bilateral cochlear implant users. Even in normal-hearing listeners the squelch effect is small (circa 3 dB).[10] In **chapter 4** we demonstrated that an apparent squelch effect occurred in the simultaneous BiCI group of our RCT. In 13 out of 19 individual patients a squelch effect was already present in at least one ear after a 1-year follow-up. On group level, we found a squelch effect in the amount of 0.6dB (not significant) after 1 year, 0.9dB after 2 years (significant) and 1.9dB (significant) after 3 years in the best performing ear. Previous cohort studies that evaluated the squelch effect after at least one year of follow-up also observed a squelch effect on group level. [5,10,14] Yet, a squelch effect could not be demonstrated after a follow-up period of only six months.[1,3,15] Therefore, it is plausible that a squelch effect

will only occur after more listening experience. Furthermore, our results show an increase of the squelch effect in the years after BiCI. Eapen et al. provided a follow-up time of 4 years of a 9 patients cohort and showed similar results, they observed an increasing squelch effect over time.[10] The growth of the squelch effect over time suggest cortical integration and differentiation of inputs from BiCI due to continued binaural processes after the first years after implantation.

1.2.4. Adequate follow-up duration

In the literature concerning BiCI reported follow-up duration ranges vary widely. As we explained in the section above, a follow-up period of at least 1 year is necessary to detect a possible squelch effect. In chapter 3 we showed that there were no significant differences for any of the reported outcomes on group level when we compared the 1-year data to the 2-year data. Therefore, in future studies regarding CI, a follow-up period of at least 1 year may be considered as a reliable evaluation period when speech and spatial hearing are concerned. However, **chapter 5** shows that a squelch effect increases over time, so if the full benefit of BiCI will be determined, an even longer follow-up period might be considered to detect these outcome improvements.

1.3. Future perspectives – Bilateral cochlear implantation

1.3.1. Sequential bilateral cochlear implantation

As explained above, in addition to the existing literature, our RCT provides evidence for important subjective and objective advantages of simultaneous BiCI compared to UCI in difficult everyday listening situations (**chapter 2** and **chapter 3**). Hopefully, Dutch insurance companies take these important findings into account and reconsider the point of view on BiCI in adults. If BiCI would become the preferred treatment for patients with severe to profound bilaterally SNHL, many patients who already received one cochlear implant in the past will become eligible for treatment with a second cochlear implant. The question arises whether the hearing results for simultaneous BiCI and sequential BiCI are comparable and after how many years after the first implantation, a second implantation in the contralateral ear will be beneficial to the full potential. Patients in the UCI group of our RCT received a second implant after 2 years. One year after the second implantation, we demonstrated that patients in the sequential BiCI group derived the same benefits as those in the simultaneous group. Patients had significant improvements in spatial speech in noise and localization abilities compared to their unilateral situation

before the second implantation.[16] These results promote the consideration of sequential BiCI in unilaterally implanted patients, in order to improve their spatial hearing and to enable sound localization performance. The effect of prolonging the inter-implant period was not investigated in this study. Since we know that spiral ganglion cells (SGCs), which are important for the perception of electrical stimulation provided by cochlear implants, will eventually degenerate after SNHL,[17] minimization of the inter-implant period in sequential BiCI seems essential. Although, there is evidence for important benefits of a second implant in postlingually deafened adults after many years.[15] Further high-quality studies are necessary to investigate the inter-implant period in sequential BiCI thoroughly.

1.3.2. Patient selection for bilateral cochlear implantation

Previous data on sequential BiCI already showed that not all patients proceed to a second implant after UCI.[18] In our RCT, also 3 out of 19 patients of the sequential BiCI group did not want to proceed to BiCI.[16] There appears to be a relation between patients' withdrawal and satisfaction with the performance of the first implant. With respect to the QoL questionnaires, there were no significant differences between the UCI and simultaneous BiCI group (**chapter 2** and **chapter 3**). Neither was there a significant improvement of QoL within the sequential BiCI group after the second implantation.[16] This can partly be explained by the fact that CI, either uni- or bilateral, will provide important benefits in daily life when compared to the situation before implantation. Although the overall hearing results will be better after either of those, some patients will be satisfied with the situation after UCI, while others would definitely benefit from a second implant. The expectations concerning hearing capabilities after CI will diverge between people. For a young healthy professional, spatial hearing and the ability to localize sounds is essential. A senior citizen with less challenging everyday listening circumstances on the other hand, could be satisfied with good performance on easy listening situations, which can be provided by unilateral implantation. In our opinion, patients' selection and expectation management is therefore important in considering bilateral implantation in adults. Adequate patient selection will therefore result in better subjective results after treatment. Future studies concerning this topic are required.

PART TWO – FUTURE INDICATIONS

TINNITUS AND COCHLEAR IMPLANTATION

2.1. Main results and conclusions per chapter – Tinnitus and cochlear implantation

Based on a systematic review, in **chapter 6**, we present an overview of the effect of UCI on tinnitus in adults with bilateral SNHL. Ten cohort studies satisfied the eligibility criteria and critical appraisal. Data could not be pooled because of a large clinical heterogeneity between these cohort studies, therefore we used a descriptive analysis of the studies instead. Overall, current literature shows a decrease of tinnitus after UCI. However, there is also a chance of increase of existing tinnitus and newly induced tinnitus was also reported.

Chapter 7 evaluates the effect of either UCI or BICI on tinnitus in adults with bilateral severe to profound SNHL. A prospective study as part of the RCT comparing simultaneous BiCI to UCI or sequential BiCI was performed. Tinnitus was evaluated before and 1 year after implantation in 38 patients with three tinnitus questionnaires; the Tinnitus Handicap Inventory (THI), the Tinnitus Questionnaire (TQ) and a visual analogue scale for tinnitus burden. Sixteen of the 38 participants had pre-operative tinnitus. In this chapter, we show that both UCI and BiCI, are effective in the reduction of existing tinnitus; THI scores decreased in 80.0% of patients and TQ scores decreased in 71.4%. Tinnitus may also increase or even be induced after cochlear implantation. Tinnitus was induced after cochlear implantation in 27.3%.

2.2. Comparison to and critical review of the literature – Tinnitus and cochlear implantation

Worldwide, millions of people experience tinnitus and their QoL can be severely affected. A strong association is found between tinnitus and SNHL, the prevalence of tinnitus is higher in these patients and in CI candidates it reaches 67% to 86%.[19] As described in **chapter 6**, the best available evidence concerning the effect of CI on tinnitus consists of non-randomized, low or moderate level of evidence studies in patients with severe SNHL who also suffer from tinnitus. Furthermore, there is a lack of studies concerning BiCI and tinnitus. As a secondary outcome of the RCT, concerning simultaneous BiCI to UCI or

sequential BiCI, we evaluated both UCI and BiCI on tinnitus perception after a 1-year follow-up in patients with bilateral SNHL (**chapter 7**). The prevalence of tinnitus in our population was lower than described in the literature, 16 out of 38 patients (42.1%) This can be explained by the fact that the standard of reporting tinnitus was inconsistent between studies. We considered a score of more than zero on either the THI or TQ as tinnitus, while other studies used self-designed questionnaires.

Chapter 7 shows that 1 year after implantation, tinnitus questionnaire scores had decreased in most patients and some patients had become completely free of tinnitus. Tinnitus decreased in 71.4% of patients according to the TQ and in 80% according to the THI. These results are in line with the results of the existing literature, which describes reduction rates varying from 64% to 100%.[20-25] Six out of 22 patients (27.3%), who did not experience tinnitus pre-implantation, did experience tinnitus post-implantation. This induction rate was higher than in the current literature which varies from 1.3% to 24.5%.[26-29] A possible reason for this could be the extensive focus on tinnitus in our study, resulting in higher tinnitus attention in our group after implantation.

After both UCI and BiCI we found a significant decrease of existing tinnitus. No significant differences in decrease were found between the groups. However, the prevalence of newly induced tinnitus was substantially higher after BiCI compared to UCI; 50% (5 out of 10) in the BiCI group versus 8.3% (1 out of 12) in the UCI group. This difference was not statistically significant. The existing literature is inconclusive about the effect of BiCI on tinnitus and contradictory results have been reported. Summerfield et al.[30] reported an increase in tinnitus burden after the second implantation, whereas Olze et al.[31] reported a decrease in tinnitus burden after the first implantation and a further decrease after the second implantation. A more recent publication of our research group showed comparable results for either simultaneous BiCI or sequential BiCI on tinnitus after a follow-up of 1 year; on group level, BiCI had a positive effect on tinnitus burden, but newly induced tinnitus was also reported.[32]

2.3. Future perspectives – Tinnitus and cochlear implantation

2.3.1. Tinnitus as main indication for cochlear implantation

As in our study (**chapter 7**), in most studies regarding the effect of CI on tinnitus the indication for implantation was hearing restoration and they were not

selected solely for the presence of tinnitus. The change in tinnitus perception was an unintentional effect of the implantation. The tinnitus burden severity in cochlear implant candidacy may be lower than in patients with severe tinnitus. Therefore, it is more difficult to measure improvement of tinnitus after implantation. Furthermore, because tinnitus was not the main reason for implantation, some important patient characteristics concerning tinnitus (e.g., side of tinnitus and on-off modus of cochlear implant) are missing. Further RCTs or well-defined prospective cohort studies with patients suffering from severe tinnitus and non-severe hearing loss are needed to provide higher level of evidence for the effect of CI on tinnitus.

2.3.2. Consensus in questionnaires concerning tinnitus therapy

The definition of outcomes for subjective tinnitus is challenging and till now, there are no common standards for measuring treatment efficacy. Pooling data in a meta-analysis is only possible with homogenous outcome measures. Therefore the Core Outcome Measures in Tinnitus (COMiT) initiative was started to establish a common standard, which identifies what specific tinnitus-related complaints ("outcome domains") are critical and important to assess in all clinical trials to determine whether an intervention has worked.[33]

Currently, most available studies concerning the effect of CI on tinnitus use either the THI or TQ. Both questionnaires measure individual differences in tinnitus burden, but they are not designed for measuring treatment-related changes in tinnitus. Therefore Meikle et al. developed the Tinnitus Functional Index (TFI).[34] The TFI is a 25-item self-report questionnaire that is validated for scaling tinnitus burden but also to measure treatment-related changes in tinnitus. Future studies concerning the effect of CI on tinnitus should use this validated questionnaire.

SINGLE-SIDED DEAFNESS AND COCHLEAR IMPLANTATION

3.1. Main results and conclusions – Single-sided deafness and cochlear implantation

Chapter 8 systematically reviews the literature on the clinical outcome of CI for patients with SSD or asymmetrical hearing loss (AHL). Nine studies satisfied

the eligibility criteria and critical appraisal. Because of large heterogeneity between studies, we were not able to pool data in a meta-analysis, therefore we summarized the extracted data per outcome critically. In conclusion, this systematic review shows that there are no high level-of-evidence studies concerning CI in patients with SSD or AHL available. Overall, current literature suggests important benefits of CI regarding sound localization, QoL and tinnitus burden in patients with hearing loss. Although results for speech perception in noise are promising as well, varying results between studies were reported for this outcome. Larger and high-quality studies are certainly warranted.

3.2. Future perspectives – Single-sided deafness and cochlear implantation

We comprehensively discussed the benefits of binaural hearing in current thesis. As a result of this knowledge, there is a growing interest for BiCI in bilaterally deafened patients. Patients with SSD also become aware of the importance of binaural hearing and till now, standard treatment options for these patients only consist of hearing improvement with either a Contralateral Routing of Signal (CROS) or a Bone Conduction Device (BCD) at the hearing impaired side. With either a CROS or BCD, binaural input cannot be restored. This restriction may be overcome by the insertion of a CI in the hearing impaired side.

Given the limited but promising results for CI for patients with SSD as discussed in **chapter 8**, larger and high-quality studies are certainly warranted before CI can be considered as standard clinical care. To compare all different treatment options for patients with SSD, in 2015, our research department started the CINGLE (CI for single-sided deafness) trial.[35] In this study, 120 adults with SSD were included and randomized to 1) CI, 2) first BCD, then CROS or 3) first CROS, then BCD. Patients in the two latter groups are able to choose if they want to continue with either BCD or CROS after the trial period. Outcomes of interest are speech perception in noise, sound localization, quality of life and tinnitus. These outcomes will be measured during a baseline visit and at follow-up visits, which will take place at 6, 12, 18, 24, 36, 48 and 60 months after onset of treatment. Furthermore, an economic evaluation will be performed to answer the question if the additional costs of CI are justified by increased benefits compared to current treatment strategies. At this moment, the CINGLE trial is still ongoing, but we assume that over time current trial will give us more clarity about this important topic.

4. Overall strengths and limitations of the prospective studies in current thesis

The major strength of **chapter 2** and **chapter 3** is that data was gathered by using a RCT. All data were collected at fixed moments. To our knowledge, this is the first RCT reporting on the benefits of simultaneous BiCI compared to UCI in adults. This way, allocation bias was minimized. A second strength is that we investigated a homogeneous study group by using strict in- and exclusion criteria. A third strength is that all 38 included patients completed the 1-year follow-up duration, during the second year of follow-up only one patient in the UCI group decided to withdraw from the study for personal reasons. Furthermore, because patients were tested after 1 and 2 years of follow-up, it was safe to assume that patients were used to their implants and that we had corrected for a possible learning effect.

Possible limitations of this RCT were that the patients were treated in five different academic clinics and the number of patients per clinic varied. By using a per center block randomization strategy we attempted to minimize this potential bias. Moreover, the researchers and practitioners were not masked. However, a strict study protocol was used to minimize testing differences among researchers.

Chapter 4, **chapter 5** and **chapter 7** were based on secondary analysis from the previous mentioned RCT. Therefore, the prospective study design is a strength, but a power analysis for these studies was not performed. Therefore, the studies may be underpowered. Furthermore, we did not control for different volume control settings among patients in **chapter 4**. They used their speech processors as in daily live.

Chapter 5 is the first study that reports whether simulated unilateral hearing (switching off one cochlear implant) provides the same results as real life unilateral hearing. At time of inclusion, all patients suffered from profound SNHL. Because of the profound hearing loss in the contralateral ear (second implanted ear) patients were not used to listening with two ears after the first implantation. Therefore, the situation before the second implantation can be considered as actual unilateral hearing.

In **chapter 7** we focus on potential changes in tinnitus perception 1 year after CI. Due to the primary aim of the RCT, we did not select patients solely for the presence of tinnitus. Only 16 of the 38 included patients had tinnitus before implantation. Therefore, our total tinnitus group had a limited size and some patient characteristics concerning tinnitus were missing (e.g., side of tinnitus and effect of on- and off modus of the cochlear implant on tinnitus perception). This way, we could not determine correlations between some patient related factors and their potential effect on tinnitus.

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CHAPTER

10

Summary in Dutch
(Nederlandse samenvatting)

Hoofdstuk 1 (algemene inleiding) beschrijft de anatomie van het menselijke oor, fysiologie van normaal horen en de pathologie van gehoorverlies. Verder worden cochleaire implantatie (CI) en de selectie criteria hiervoor besproken. Unilaterale cochleaire implantatie (UCI) is een algemeen aanvaarde behandelingsmodaliteit voor volwassenen met ernstig bilateraal perceptief gehoorverlies. We benoemen de voordelen van het horen met twee oren (binauraal horen) en leggen uit dat dit gebaseerd is op drie belangrijke principes: het hoofdschaduw effect, het binaurale summatie effect en het squelch effect. Deze kennis ondersteunt de groeiende interesse in bilaterale cochleaire implantatie (BiCI). Hoewel eerdere studies al voordelen van BiCI in vergelijking met UCI aantoonden, wordt in Nederland in de meeste gevallen slechts één cochleair implantaat vergoed door de verzekeringsmaatschappij. Dit in tegenstelling tot sommige andere Europese landen waar bilaterale implantatie in postlinguaal dove volwassenen de behandeling van eerste keus is geworden. Één van de redenen voor deze discrepantie is het tekort aan kwalitatief goed onderzoek. Onze studiegroep is daarom gestart met een gerandomiseerd gecontroleerd onderzoek (randomized controlled trial [RCT]) waarin we simultane BiCI vergelijken met UCI danwel sequentiële BiCI in postlinguaal dove volwassenen. Patiënten in de sequentiële groep werden in eerste instantie geïmplanteerd met één cochleair implantaat en na 2 jaar ontvingen zij hun tweede implantaat. ***Deel één*** van dit proefschrift presenteert resultaten van deze RCT. In ***deel twee*** richten we ons op toekomstige indicaties voor CI. Tinnitus is een vaak voorkomende en invaliderende klacht in patiënten met ernstig perceptief gehoorverlies. De beschikbare literatuur laat over het algemeen een afname van tinnitus zien na CI. Tot slot geven we informatie over actuele behandelingsmodaliteiten van eenzijdige doofheid en wordt de potentiële toekomstige rol van CI in deze groep patiënten benoemd.

DEEL ÉÉN – BILATERALE COCHLEAIRE IMPLANTATIE

Hoofdstuk 2 presenteert de eerste resultaten van de RCT waarin we BiCI met UCI vergelijken na 1 jaar follow-up. Achtendertig postlinguaal dove volwassenen werden in deze studie geïncludeerd en gerandomiseerd over twee groepen; simultane BiCI danwel UCI. De primaire uitkomstmaat was spraak in ruis waarin zowel de spraak als de ruis van recht vooruit werd aangeboden (U-STARR). Secundaire uitkomstmaten waren: spraak in ruis vanuit verschillende richtingen (SISSS), spraakverstaan van woorden in stilte (CNC-test), lokaliseren van

geluiden en vragenlijsten over kwaliteit van horen. Na 1 jaar follow-up werden geen significante verschillen gemeten tussen de groepen met de U-STARR of CNC-test. Patiënten in de BiCI groep presteerden wel significant beter dan patiënten uit de UCI groep wanneer spraak en ruis vanuit verschillende richtingen werd aangeboden (SISSS). Ook konden patiënten in de BiCI groep geluiden lokaliseren, dit was voor patiënten in de UCI groep onmogelijk. Deze objectieve resultaten kwamen overeen met de zelf-gerapporteerde uitkomsten van de vragenlijsten over kwaliteit van horen. Dit hoofdstuk laat zien dat BiCI significante voordelen biedt boven UCI in dagelijkse luistersituaties in postlinguaal dove patiënten.

In **hoofdstuk 3** presenteren we de resultaten van de RCT waarin we BiCI met UCI vergelijken na 2 jaar follow-up. Wederom presteerden patiënten in de simultane BiCI groep significant beter dan patiënten in de UCI groep wanneer spraak en ruis vanuit verschillende richtingen werden aangeboden. Daarnaast waren patiënten na bilaterale implantatie in staat om geluiden te lokaliseren. Net als na 1 jaar follow-up werden ook na 2 jaar follow-up vergelijkbare resultaten voor beide groepen gezien met de U-STARR en CNC-test. De objectieve resultaten kwamen overeen met de zelf-gerapporteerde uitkomsten met betrekking tot de vragenlijsten over kwaliteit van horen. Er werden geen significante verschillen gevonden tussen de twee groepen op de kwaliteit van leven vragenlijsten. Dit hoofdstuk illustreert net als voorgaand hoofdstuk belangrijke voordelen van simultane BiCI in vergelijking met UCI, deze voordelen blijven aanwezig in het tweede jaar na CI. Hypothetisch zouden de resultaten van de gehele studie groep na 2 jaar implantaat gebruik kunnen verschillen van de resultaten na 1 jaar gebruik, dit door een toenemende leercurve. We hebben dit in onze studiepopulatie onderzocht door gebruik te maken van een “within subject” ontwerp, er werd echter voor geen enkele uitkomst een significant verschil gevonden na 2 jaar follow-up in vergelijking met 1 jaar follow-up. Aangezien er geen bewijs is voor verdere groei in het tweede jaar na implantatie, beschouwen we een follow-up duur van 1 jaar als een betrouwbare evaluatie periode in CI studies.

Hoofdstuk 4 evalueert het optreden van een squelch effect in de eerste 3 jaren na simultane BiCI. We voerden een prospectieve studie uit als onderdeel van de RCT waarin simultane BiCI wordt vergeleken met UCI danwel sequentiële BiCI. In de simultane BiCI groep werd het squelch effect op jaarlijkse basis gemeten met de SISSS. We vergeleken de bilaterale resultaten met de unilaterale

resultaten door het implantaat aan de ruis zijde uit te zetten. Het squelch effect werd onderzocht voor het best presterende oor en voor het linker en rechter oor afzonderlijk. Na 2 jaar toonden we een meetbaar voordeel aan op basis van het squelch effect in het best presterende oor, dit voordeel nam verder toe na 3 jaar. Na 3 jaar werd er een squelch effect aangetoond in beide oren. Actuele observaties suggereren dat de hersenen na simultane BiCI gebruik maken van interaurale verschillen om spraak van ruis te onderscheiden. Doordat het squelch effect groeit met de jaren, is het aannemelijk dat er nog verdere ontwikkeling van corticale integratie en differentiatie plaats zal vinden na de eerste jaren na implantatie.

In **hoofdstuk 5** onderzoeken we of gesimuleerd unilateraal horen (uitzetten van één cochleair implantaat) vergelijkbare resultaten geeft als daadwerkelijk unilateraal horen met één cochleair implantaat en een niet-geïmplanteerd contralateraal oor. In de reeds bestaande literatuur wordt de unilaterale luistersituatie regelmatig gesimuleerd door één implantaat uit te zetten in bilateraal geïmplanteerde patiënten. Dit hoofdstuk beoordeelt of dit een accurate test methode is door gebruik te maken van de data van de sequentiële BiCI groep van de eerder besproken RCT. De primaire uitkomstmaat was spraak in ruis waarin zowel de spraak als de ruis van recht vooruit werden aangeboden. Secundaire uitkomstmaten waren: spraak in ruis vanuit verschillende richtingen (SISSS), spraakverstaan van woorden in stilte (CNC-test) en lokaliseren van geluiden. Resultaten van het horen met één cochleair implantaat en een niet-geïmplanteerd oor (1 en 2 jaar follow-up) werden vergeleken met het gesimuleerde unilaterale horen in de sequentiële BiCI groep waarbij één implantaat werd uitgezet (3 jaar follow-up). Er werden geen significante verschillende gevonden voor de verschillende uitkomsten na 1, 2 danwel 3 jaar follow-up. In dit hoofdstuk laten we zien dat gesimuleerd unilateraal horen door één implantaat uit te zetten in bilaterale CI gebruikers een betrouwbare testmethode is om unilateraal en bilateraal horen met elkaar te vergelijken.

DEEL TWEE – TOEKOMSTIGE INDICATIES

In **hoofdstuk 6** geven we op systematische wijze een overzicht van de beschikbare literatuur met betrekking tot het effect van UCI op tinnitus in volwassenen met ernstig bilateraal perceptief gehoorverlies. Tien cohort studies kwamen door het selectie proces en werden geïncludeerd voor verdere

analyse. Vanwege de grote heterogeniteit tussen studies en de afwezigheid van studies met een hoog niveau van bewijsvoering (level of evidence) was poolen van de data van de diverse studies in een meta-analyse niet wenselijk, als alternatief hebben we een beschrijvende analyse van de studies weergegeven. Over het algemeen laat actueel beschikbare literatuur een afname van tinnitus zien na UCI. In een minderheid van de patiënten wordt echter ook progressie van bestaande tinnitus of nieuw geïnduceerde tinnitus beschreven.

Hoofdstuk 7 evalueert het effect van UCI danwel BiCI op tinnitus in patiënten met bilateraal ernstig tot zeer ernstig perceptief gehoorverlies. Wij voerden een prospectieve studie uit als onderdeel van de RCT waarin simultane BiCI wordt vergeleken met UCI danwel sequentiële BiCI. Tinnitus werd pre-operatief en 1 jaar na implantatie beoordeeld in 38 patiënten op basis van drie verschillende vragenlijsten: de "Tinnitus Handicap Inventory" (THI), de "Tinnitus Questionnaire" (TQ) en op basis van een visuele analoge schaal (VAS) voor tinnitus.

Bij 16 van de 38 deelnemers was er sprake van pre-operatieve tinnitus. In dit hoofdstuk laten we zien dat zowel UCI als BiCI effectief zijn in het reduceren van reeds bestaande tinnitus; THI waarden daalden in 80.0% van de patiënten en TQ waarden in 71.4%. Daarentegen rapporteren we ook dat tinnitus in ernst kan toenemen na CI en dat er in sommige gevallen zelfs sprake is van nieuw geïnduceerde tinnitus. Tinnitus werd in 27.3% van de patiënten geïnduceerd.

In **hoofdstuk 8** beoordelen we op een systematische wijze de bekende literatuur met betrekking tot het effect van CI in patiënten met eenzijdige doofheid of asymmetrisch gehoorverlies. Negen studies voldeden aan de inclusie criteria en voltooiden een kritische beoordeling op kwaliteit met succes. Grote heterogeniteit tussen de studies maakte het poolen van data in een meta-analyse onmogelijk en daarom waren we genoodzaakt om de geëxtraheerde data samenvattend weer te geven per uitkomst. Concluderend laat deze systematische review zien dat er geen studies beschikbaar zijn met een hoog niveau van bewijsvoering (level of evidence). Actuele literatuur suggereert belangrijke voordelen van CI met het oog op lokaliseren van geluiden, kwaliteit van leven en tinnitus. Resultaten voor spraakverstaan in ruis lijken ook veelbelovend, er worden echter wisselende resultaten per studie gerapporteerd voor deze uitkomstmaat. Grotere studies en onderzoek van hogere kwaliteit naar het effect van CI in patiënten met eenzijdige doofheid of asymmetrisch gehoorverlies is absoluut noodzakelijk.

Hoofdstuk 9 (discussie) vat de resultaten uit voorgaande hoofdstukken van dit proefschrift samen en vergelijkt deze met de reeds beschikbare literatuur. Samenvattend toont dit proefschrift belangrijke voordelen van BiCI ten opzichte van UCI in dagelijkse luistersituaties in postlinguaal dove patiënten. Deze voordelen blijven aanwezig in het tweede jaar na CI. Deze resultaten zijn verkregen door een RCT uit te voeren, waardoor een aantal soorten bias voorkomen worden en dus een belangrijke toevoeging wordt geleverd aan de reeds beschikbare literatuur. Daarnaast tonen we aan dat er aanwijzingen zijn voor het optreden van een squelch effect na bilaterale implantatie. Het squelch effect lijkt toe te nemen met de tijd, het is daarom aannemelijk dat er nog verdere ontwikkeling van corticale integratie en differentiatie plaats zal vinden na de eerste jaren na implantatie. Verder wordt er binnen onze RCT over het algemeen een reductie van tinnitus gezien na CI, echter rapporteren we ook dat tinnitus in ernst kan toenemen na implantatie en dat er in sommige gevallen zelfs inductie van tinnitus op kan treden. Deze bevindingen komen overeen met de reeds aanwezige literatuur op dit gebied. Nader gespecificeerd onderzoek naar het effect van CI op tinnitus is noodzakelijk voordat CI als een behandelingsmodaliteit voor tinnitus mag worden beschouwd. Door de kennis over de voordelen van bilaterale implantatie in postlinguaal dove patiënten is er ook een groeiende interesse voor CI bij patiënten met eenzijdige doofheid. Actuele literatuur suggereert belangrijke voordelen in deze patiëntengroep. Grotere studies en onderzoek van hogere kwaliteit is echter noodzakelijk voordat we hier conclusies aan mogen verbinden. Ten slotte bediscussiëren we in dit hoofdstuk de sterktes en beperkingen van het onderzoek in huidig proefschrift en worden suggesties gegeven voor toekomstig onderzoek met betrekking tot CI.

APPENDICES

LIST OF ABBREVIATIONS

AHL	Asymmetrical hearing loss
BCD	Bone conducting device
BiCI	Bilateral cochlear implantation
CI	Cochlear implantation
CONSORT	Consolidated standards of reporting trials
CNC	Consonant-nucleus-consonant
CROS	Contralateral routing of signal
dB	Decibel
EQ-D5	European quality of life questionnaire D5
FU	Follow-up
HA	Hearing aid
HC	Hair cell
HUI3	Health Utilities Index 3
IHC	Inner hair cell
NCIQ	Nijmegen cochlear implant questionnaire
NS	Not significant
OHC	Outer hair cell
PTA	Pure-tone audiometry
QoL	Quality of life
SD	Standard deviation
SGC	Spiral ganglion cell
SISSS	Speech intelligibility in noise with spatially separated sources
SNR	Signal to noise ratio
SNHL	Sensorineural hearing loss
SPL	Sound pressure level
SRTn	Speech reception threshold in noise
SSD	Single-sided deafness
SSQ	Speech, spatial, and qualities hearing scale
TTO	Time trade-off
UCI	Unilateral cochlear implantation
U-STARR	Utrecht - sentence test with adaptive randomized roving levels
VAS	Visual analog scale

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ABOUT THE AUTHOR

Alice van Zon was born on the 21st of August 1987 in Heerlen, the Netherlands. After graduation from Gymnasium (Sintermeertencollege) in 2005, she moved to Utrecht to study medicine at Utrecht University.

During her medical study she combined her interest in health care and traveling by spending some time abroad. She went to Nepal for a clerkship ophthalmology (Himalaya Eye Clinic, Pokhara), worked in South Africa for a clerkship trauma surgery (Tygerberg Hospital, Cape Town) and visited the United Kingdom for an extracurricular clerkship otorhinolaryngology (Royal National Throat Nose Ear Hospital, London).

In the final year of her medical study she decided to pursue a career in Ear Nose Throat (ENT) surgery. She spent six months at the department of Otolaryngology and Head & Neck surgery of the UMC Utrecht and she started a research project at the Wilhelmina Children's Hospital. In addition, she performed a Cochrane systematic review on the effects of antibiotics in children with otitis media with effusion, for which she received a Cochrane Incentive Award.

In 2012 she obtained her medical degree, upon she started working as a surgical resident at the Ter Gooi Hospital in Hilversum and Blaricum. In this period she moved to Amsterdam, where she still lives and enjoys the vibrant city life, and her hobbies cycling, yoga, kitesurfing and other sports.

At the beginning of 2013, she started the PhD project that led to this thesis at the department of Otorhinolaryngology and Head & Neck surgery of the UMC Utrecht.

One year later, in 2014, her residency started at the UMC Utrecht supervised by Drs. I. Ligtenberg – van der Drift, Prof. Dr. R.J. Stokroos and Prof. Dr. W. Grolman. During her residency, she completed part of her training at the St. Antonius Hospital, Nieuwegein / Utrecht (supervised by dr. M.P. Copper), the Meander MC, Amersfoort (supervised by Prof. Dr. H.F. Mahieu), the Gelderse Vallei, Ede (supervised by Dr. M.H.J.M. Majoor) and the Gelre Hospital, Apeldoorn (supervised by Dr. Tj. D. Bruintjes).

In 2019, she became a medical specialist in ENT, after which she started working at the St. Antonius hospital in Nieuwegein / Utrecht.