A Study Protocol for a Randomised Controlled Trial Evaluating the Benefits from Bimodal Solution with Cochlear Implant and Hearing Aid vs. Bilateral Hearing Aids in Patients with Asymmetric Speech Identification Scores.

Trial Registration Number: NCT04919928 (ClinicalTrials.gov)

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A Study Protocol for a Randomised Controlled Trial Evaluating the Benefits from Bimodal Solution with Cochlear Implant and Hearing Aid vs. Bilateral Hearing Aids in Patients with Asymmetric Speech Identification Scores.

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Abstract

Introduction

Cochlear implant (CI) and hearing aid (HA) in a bimodal solution (CI + HA) is compared to bilateral HAs (HA +HA) to test if the bimodal solution result in better speech intelligibility and self-reported quality of life.

Methods and Analysis

This randomised controlled trial (RCT) is conducted in Odense University Hospital, Denmark. Sixty adult bilateral HA users referred for CI surgery is enrolled if eligible and undergo: audiometry, speech perception in noise (HINT: Hearing in Noise Test), Speech Identification Scores (SIS) and video head impulse test (v-HIT). All participants will receive new replacement HAs. After one month they will be randomly assigned (1:1) to the intervention group (CI+HA) or to the delayed intervention control group (HA+HA). The intervention group (CI+HA) will receive a CI on the ear with a poorer speech recognition

score and continue using the HA on the other ear. The control group (HA+HA) will receive a CI after a total of 4 months of bilateral HA use.

The primary outcome measures are Speech intelligibility measured objectively with HINT (sentences in noise) and DANTALE I (words) and subjectively with the Speech, Spatial and Qualities of Hearing scale questionnaire (SSQ-12). Secondary outcomes are patient reported Health-Related Quality of Life (HRQoL) scores assessed with the Nijmegen Cochlear Implant Questionnaire (NCIQ), the Tinnitus Handicap Inventory (THI) and Dizziness Handicap Inventory (DHI). Third outcome is listening effort assessed with pupil dilation during HINT

In conclusion, the purpose is to improve clinical decision-making for CI candidacy and optimize bimodal solutions.

Ethics and Dissemination

This study protocol was approved by the Ethics Committee Southern Denmark project ID S-20200074G. All participants are required to sign an informed consent form.

This study will be published upon completion in a peer-reviewed publications and scientific conferences.

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Strengths and Limitations of This Study

- The study uses comprehensive measures of self-reported outcomes as well as objective tests of speech intelligibility.
- Listening effort controlled with pupillometry during objective tests of speech intelligibility.
- Open label RCT (blinding is not possible due to visibility of the CI).
- Possible large drop rates if new HAs improve speech intelligibility to an extent that CI treatment is rejected or postponed.

Introduction

Background

Cochlear implants (CIs) have been used to restore hearing in individuals with severe to profound sensorineural hearing loss. Initially, most patients receiving a cochlear implant were profoundly deaf in both ears. (1, 2) However, recently it has become more common to implant patients with significant residual hearing in the affected ear, as well as in patients with asymmetric hearing loss and single-sided deafness, with significant residual hearing or normal hearing on the contralateral side.(3, 4) A CI in one ear and a HA in the other ear can provide enhanced hearing performance in patients with asymmetrical hearing.(5, 6) The combination of CI and HA is referred to as bimodal hearing or bimodal solution.(7)

CI Candidacy

In the UK, The National Institute for Health and Care Excellence (NICE) have listed guidelines for cochlear implantation and recommends that unilateral CI is offered to patients

with severe to profound deafness who do not receive adequate benefit from acoustic hearing aids. Severe to profound deafness is defined as pure-tone audiometric threshold ≥ 80 dB HL at 2 or more frequencies (500 Hz, 1,000 Hz, 2,000 Hz, 3,000 Hz and 4,000 Hz). Another criteria is that SIS< 50% in the ear considered for implantation and in best aided condition SIS≤60%(8).

The Danish CI candidacy criteria consists of SIS (without HAs, measured with headphones) ≤45% and a SIS ≤65% (in best aided condition) in the ear considered for implantation using DANTALE I monosyllabic word-lists.(9) Additional testing to evaluate speech understanding is assessed by HINT.(10, 11)

The recommendation for a CI might be less clear for patients with asymmetric hearing because they may not fall into the traditional referral criteria but would likely benefit from a CI. It is therefore necessary to establish more evidence to support the effectiveness of bimodal CI+HA versus HAs in patients with asymmetric hearing.

Bimodal Solution vs. Bilateral HAs

Normal hearing listeners (NH) benefit from listening with two ears, which help them understand speech in noise and identify sound location.

Benefits from listening with two ears include: head shadow effect, binaural summation, binaural squelch, localization and spatial release from masking.(12-15)

Patients with hearing loss often do not have these benefits, and they are often not accessible to CI patients. (15)Many bimodal CI and HA users are missing these benefits because the devices are unsynchronized.(16)

Until now it is unknown when to introduce the bimodal solution and making sure that patients are well-fitted with hearing aids when they are given the candidacy assessment.

The question is if the bimodal benefits are bigger than the bilateral hearing aid condition when they are well fitted?

This study will therefore support and strengthen the preoperative clinical decision to recommend a bimodal solution with a CI and a HA versus the continuous use of bilateral HAs. This may offer the patient faster and more effective treatment because delaying the surgery may not be beneficial.

Patient-Reported Outcome Measures

Benefits of the CI are measured subjectively with Patient-Reported Outcome Measures (PROMs) as SSQ12, NCIQ, THI and DHI.(17-24)

The validity and reproducibility of the Danish version of THI has been reported(24). SSQ12, DHI, NCIQ have all been translated into Danish and backward translated to English following a cultural adaption and pilot-testing to ensure correct understanding of the questionnaires. Test-retest reliability has been assessed as well.(18, 20, 22)

Listening Effort

Patients with CI often experience high levels of listening effort, they often report that understanding speech causes high levels of increased sustained effort which results in feelings of fatigue.(25) These feelings may lead patients to withdraw socially due to the stresses involved in communication even though they may not specifically report difficulties with speech understanding.(19)

Effort in listeners with NH can be reflected by the relationship between speech intelligibility and pupil-dilation.(26) Listening effort has been defined as the “Deliberate allocation of

mental resources to overcome obstacles in goal pursuit when carrying out a task" and is the basis for the Framework for Understanding Effortful Listening (FUEL) model.(27) Understanding speech in challenging hearing environments results in increased auditory and cognitive processing which can be observed objectively by measuring the pupil dilation during speech perception in noise, in a task such as the HINT(28-30)

Rationale and Objectives

This randomised controlled trial is designed to improve clinical decision-making for CI candidacy for patients with asymmetric hearing. It is necessary to establish more evidence to support the effectiveness and the fitting optimization of bimodal CI+HA versus HAs in patients with asymmetric hearing.

The first objective of the study is to evaluate the subjective (SSQ12) and objective (Hearing In Noise Test (HINT) which is word and sentence based and DANTALE I, which is monosyllabic word-based) benefits of a bimodal solution (CI+HA) compared to (HA+HA).

The second objective is to compare and evaluate patient self-reported outcomes with NCIQ, THI and DHI in the intervention group (CI+HA) with the control group (HA+HA).

The third objective is to evaluate if listening effort, hypothesized to cause fatigue, can be measured objectively by HINT with pupillometry.

To minimize listening effort and optimize the fitting of bimodal solution the CI fitting and loudness balancing on individual level will be evaluated.(2, 31, 32)

Methods and Analysis

Study Design, Ethics and Registration

This study is a prospective randomised controlled trial based on a single centre conducted in Odense University Hospital, Denmark. The study started 01/02/2022 and is expected to end 30/07/2024. It was successfully registered at ClinicalTrials.gov with registration number: NCT04919928.

This study has been approved at Research Ethics Committee Southern Denmark (Projekt-ID: S-20200074G) 21st August 2020 to 31st December 2024.

Study Population

Sixty participants with bilateral hearing-loss and asymmetric speech identification scores referred for CI surgery will be included (Figure 1).

Inclusion Criteria

- Adults >18 years old.
- Fluent in Danish, including reading and writing
- Acquired post-lingual deafness
- Use of bilateral HAs for at least one year prior to evaluation for cochlear implantation candidacy. This to ensure, that both ears have received auditive stimulation
- PTA > 40 dB HL in the ear considered for CI implantation and PTA≥40 and ≤ 70dB HL in the contralateral ear in best aided condition, in quiet and in noise and in free field.

- SIS <70% in best aided condition in the ear considered for CI implantation and SIS ≥30% and ≤70% in best aided condition in the contralateral ear, in quiet and in noise and in free field.

Exclusion Criteria

- Vestibular loss in the ear not considered for CI implantation
- Surgical issues interfering with the site of implantation or anatomical contraindications such as cochlear malformations, which will be determined using MRI or CT-scans.
- Auditory nerve lesions.
- Central auditory pathway pathologies.
- Otosclerosis.
- Single sided deafness (SSD).

Setup

A timeline of the study is shown in (Figure 2).

All enrolled participants will be tested with audiometry and v-HIT to determine hearing thresholds and status of balance function during the first visit. Patients will receive new replacement HAs. These HAs will be fitted during the second visit and if necessary refitted at every visit in the clinic throughout the study. The baseline measurements will be conducted when both groups have used the new replacement HAs to ensure acclimatisation. The measurements are SIS in quiet and in noise with a signal-to-noise ratio (SNR) of 0dB using DANTALE I speech material. The speech and masking white noise

stimulus will be presented at 65 dB SPL in the free field. Stimuli will be presented as auditory stimuli only as well as with visual cues, the latter to allow participants to use lipreading cues. Pupillometry variables are Peak Pupil Dilation (PPD), Mean Pupil Dilation (MPD), peak-time and standard deviation using HINT (sentences and words).

The HINT sentences are presented at a speech level of 65dB and initially an adaptive SNR is used to identify the SNR of 70% correct word recognition. The SNR at 70% correct word recognition is used as a fixed SNR during HINT test. The noise is multi-talker babble noise, in free field, tested in best aided condition. The pupillometry glasses is the Oticon Medical Pupil Labs glasses.

Recruitment, Stratification, Randomisation and Allocation

All eligible participants will sign a written, informed consent in clinic after receiving verbal and written study information in Danish. The Danish consent form is available online at the Odense University Hospital Research Unit website.(33)

To ensure acclimatisation, participants will receive new replacement HAs fitted with the National Acoustic Laboratories (NAL) -non-linear (NL)2 fitting algorithm one month before the experiment.

They will then undergo stratification, depending on the hearing thresholds. One group will consist of participants with PTA ≥ 70dB HL; and the other group will consist of subjects with PTA ≤ 70dB HL and ≥ 40 dB HL according to the inclusion criteria. The reason for this stratification is because pre-operative hearing thresholds may affect the measured outcomes in the study. Stratification ensures that both the intervention group and the control group will have an equal distribution of patients with profound hearing loss on the ear considered for implantation.

Then the participants will be randomly allocated into two groups: the intervention group (CI+HA) and the control group (HA+HA) according to 1:1 ratio using a blocked randomisation with randomly varying block size (4 or 6).

This randomisation will be accomplished using a computer-generated random sequence in Research Electronic Data Capture (REDCap), hosted by Odense Patient Explorative Network (OPEN) in the Region of Southern Denmark and developed by Vanderbilt University, Nashville, Tennessee, United States.(34)

REDCap will also be used to send out the questionnaires to the participants´ online mailbox (called Eboks in Denmark) throughout the study (see timeline (Figure 2)) and automatically save the data.

Participants will have the opportunity to return to their original HAs if they prefer to do so after one-month of acclimatisation.

Control Group

Thirty patients, who will be age-matched, randomised and allocated to the control group HA+HA will continue the use of the new replacement HAs for another three months (total four months of new replacement HA+HA use), serving as the delayed intervention control group.

Intervention Group

Thirty patients, who will be age-matched, randomised and allocated to the intervention group CI+HA will undergo surgery as soon as possible after the HA acclimatisation period.

HA Fitting

The participant will receive either Phonak (Phonak Link M) or GN (ReSound LiNX Quattro or Resound ENZO Q) based on their personal preference. Both these HA models can be fitted with a CI by Advanced Bionics and Cochlear, respectively.

The HAs will be fitted according to NAL-NL2 procedures prescriptive fitting formula, which optimizes audibility in the bimodal solution(2) and will be verified with REM (Real Ear Measurement) to ensure that the HA is providing adequate gain and then further adjusted for comfort based on patient feedback.(35)

The new HAs will be prescribed to the patients free of charge and future service will also be free of charge.

Participants can drop out of the study if they do not want CI surgery. Collected data will be analysed if the patient still consents.

CI fitting

The CI will be selected depending on the participant´s HA selection; that is, the CI that is compatible with the HA will be selected in order to ensure the most optimal bimodal fitting.

One-month post-surgery, the CI will be activated according to the settings and stimulation strategy based on patient´s feedback. The CI will then be fitted with the HA according to the bimodal fitting formula allowing the HA to keep the NAL-NL2 fitting along with the wireless connection with the CI. (36, 37)

Patients hearing thresholds will be tested on CI activation day. The residual hearing will not be stimulated in this study.

All participants are offered standard rehabilitation with a speech therapist, including three visits a week up to 10 weeks following the initial fitting.

The training focuses on learning to identify different sounds from the environment and word discrimination.

The new CI will also be prescribed to the patients free of charge and future service will be free of charge as well.

Loudness Balancing

At 3- months follow-up the post-surgery complications will be evaluated and the levels in the CI will be adjusted if necessary.

In the loudness balancing procedure, the patient will have both the hearing aid and CI activated and at the 6-month follow-up, when the CI mapping levels are stable, patients will be randomised and assigned to one of three bimodal fitting groups:

Group A) will not complete any specific loudness balancing procedures, CI and HA will be fitted based on individual feedback from the patient.

Group B) will be fitted/finetuned using a bimodal loudness balancing task at a medium input level and adjusted based on the patient feedback. The audiologist will present a mid-level sound (approx. 55dB SPL (sound pressure level)) at the center-speaker.

Group C) will be fitted/finetuned using a bimodal loudness balancing task as group B but the audiologist will play three levels and adjust the gain for three input levels (soft, medium, and loud) according to the patient feedback.

For both groups B and C, the patient will be given a ‘Bimodal Fusion’ illustration (see Figure 3) and asked to provide feedback about the location of the sound by tracing over the line of

the head. The HA gain will be adjusted using the bimodal adjustment option until the patient reports that the sounds are perceived at the center of the head.(24)

Primary Outcome

Primary outcomes are Speech intelligibility scores measured objectively with HINT (sentences and words) and DANTALE I and subjectively with Speech, Spatial and Qualities of Hearing scale (SSQ-12). (9, 10, 22)

Secondary Outcome

Patient reported outcomes scores assessed with the Nijmegen Cochlear Implant Questionnaire (NCIQ), The Tinnitus Handicap Inventory (THI) and Dizziness Handicap Inventory (DHI). (18, 20, 24)

Third Outcome

Listening effort assessed with pupil dilation with HINT.(10)

Statistics

Power calculation

Power calculations with a power of 0.8 with a significance level of 0.05 have been made with STATA IC-15 using standard deviations for the HINT test and expected effect size (38) the NCIQ(18), and the SSQ (internal communication with BEAR (Better Hearing Rehabilitation) study on hearing aid use in Denmark) (Table 1). An estimated within participant standard deviation from the BEAR study of 1,9 in an HA population using the

SSQ-12 is used to calculate the sample size. A difference of 1,4 will require 30 participants in each arm. The effect size is expected to be larger in the CI group which will lower the number of required subjects even further.

Based on this, 30 participants must be enrolled in each arm. Additional six patients (20%) in each arm will be enrolled in the study to account for dropouts.

Test	SD pre	SD post	Expected difference between the two treatment arms	Minimum required group size
1. HINT	6.3%	6.3%	5%	26
2. NCIQ – basic sound perception	14.4	23.5	53	4
2. NCIQ	13.4	19.6	34	6
2. NCIQ – speech perception	18.8	17.8	17	20
2.NCIQ Self-esteem	20.1	16.4	22	13
2.NCIQ Activity	23.0	15.9	27	10
2.NCIQ Social Interactions	19.8	14.5	25	9
3. SSQ Total	1.9	1.9	1.4	30

Table 1: Power calculations for the desired tests. Estimated within participant standard deviations (SD pre and SD post) with expected difference and the calculated required group size.

Definition of Analysis Sets

Strategy for intention to treat analysis with incomplete observations.(39)

1. Attempt to follow-up on all randomised participants, even if they withdraw from allocated treatment.
2. Perform a main analysis of all observed data that are valid under a plausible assumption about the missing data.
3. Perform sensitivity analyses to explore the effect of deviations from the assumption made in the main analysis.
4. Account for all randomised participants, at least in the sensitivity analyses.

Analysis specification

A constrained linear mixed model is used to analyse the outcome.

The model will include randomisation group (CI+HA / HA+HA) and time (baseline/follow-up) and their interaction as fixed effects along with the threshold strata that were used in stratifying the randomisation. The model is constrained so that the mean at baseline agrees across the two treatment groups adjusted for threshold stratum, which is reasonable due to the randomisation of implant fitting. Patient ID will be included as a random effect to account for the repeated measurements.

Secondary outcomes will be analysed analogously in a constrained linear mixed model adjusting for randomisation strata. Model validation checks will be undertaken as described above, switching to bootstrapping the standard errors when model assumptions are rejected.

Covariates such as age and gender will be included in all models.

Sensitivity analysis

Inclusion is performed conditional on Pure Tone Average (PTA) (from 0.5 to 4 kHz) PTA > 40 dB HL and SIS <50% in the ear considered for CI implantation and <70% in the best-aided condition which may lead to a truncation effect in the distribution of baseline measurements. To address this, an analysis of covariance (ANCOVA) model conditioning on the baseline will be used to obtain a sensitivity analysis estimate for the main outcome.(40)

The statistical analysis plan is attached as “supplementary file” along with the Data Description listed in Appendix A.

Patient and Public Involvement

A focus-group interview was established with six cochlear implant patients. The patients commented on their decision to transition from HA to CI. Based on the feedback from the focus group, the research questions were developed.

The patients also reported problems with adjustments of the CI, when meeting the audiologist for CI adjustment controls.

Ethics and Dissemination

Ethics approval for the conduct of this study was obtained from the Ethics Committee Southern Denmark, 21st August 2020 project ID S-20200074G.

The project is approved by the Danish Data Protection Agency (file no. 20/22868) in Region South Denmark.

All participants are treated according to current clinical standards regardless of the randomised study participation. The participants are volunteers and can at any moment withdraw their participation in the study without affecting their current or future treatment rights.

The Informed Consent form will be found online as an online supplementary file and it will be signed by all participants willing to participate the study and stored in their electronic journals in Department of Audiology, Odense University Hospital. All patients are given both oral and written information about the study.

Results

Results will be presented at national and international congresses and published in the scientific literature for the attention of professional and scientific audiences on behalf of all study sites and collaborators. A lay summary report will be published for patients and members of the public.

Footnotes

Authors' Contributions:

YJ and JHS are involved in the conception of the study. LCA and JHS wrote the grant application. LCA and JHS wrote the draft of the manuscript. JHS designed and revised the draft of the methodological content. YJ reviewed and JHS critiqued the manuscript. YJ and JHS approved the final manuscript6

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Competing Interests:

None declared

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Protocol and Registration:

This study is registered in ClinicalTrials.gov: NCT04919928

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