An assessment of contemporary bone conduction devices

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An assessment of contemporary bone conduction devices

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contents

chapter 1

General introduction

A bone conduction hearing implant is a partially implantable hearing aid system, which makes use of the ability to transfer sound through bone conduction. The field of bone conduction hearing implants is rapidly evolving over the past years and the most recent developments within this field are discussed in this thesis. A variety of topics within the field are studied, from advances in implant technology and surgical procedures, to evaluation of clinical and audiological outcomes. In order to understand the functioning of a bone conduction hearing implant, it is important to first shortly discuss the physiology and pathophysiology of (bone conduction) hearing and the concept of the bone conduction hearing implant systems. This introduction aims to give a concise description of these topics.

Air and bone conduction physiology

Auditory stimulation can occur by either means of air or bone conduction. Both pathways result in a stimulation of the inner ear or cochlea and consequential excitation of the cochlear nerve. In air conduction (AC) a sound pressure wave (defined by its frequency in Hertz and amplitude in decibels) is transmitted through the outer ear canal, via the middle ear to the inner ear. More specific, the sound vibrations are captured by the auricle and directed onwards by the external acoustic meatus to the tympanic membrane (Figure 1). The mechanical vibrations from the tympanic membrane are transmitted via the three middle ear ossicles (malleus, incus and stapes) to the oval window at the cochlea. Here the mechanical vibrations are converted in a longitudinal fluid wave of perilymph within the two scalae or chambers of the cochlea, the scala vestibuli and scala tympani, and reaches onto a second membrane-covered opening of the cochlea, the round window. Transmission of the mechanical fluid waves into nerve signals takes place in the cochlea at the basilar membrane in the third scala, the scala media. The fluid wave causes the membrane to vibrate and the amplitude of the fluid wave will have a peak at a distinct distance from the oval and round window, related to the frequency of sound. At the location of maximal amplitude, the sensory hair cells of the organ of Corti at the basilar membrane are excited, causing action potentials that are transmitted to the brain via the auditory nerve (Figure 1).

Bone conduction can cause a pressure wave of the perilymph in the cochlea similar to that or air-conducted sound, also resulting in a vibration of the basilar membrane and consequently causing an action potential transmitted via the auditory nerve [1]. Mechanical vibrations of the skull result in a perilymph wave as a result of inertia of the cochlear fluid. This mechanism is considered the most dominant contributor to bone conduction perception. The perilymph wave in the scalae is a result of compliance of the oval and round window. Furthermore, alteration of the cochlear space by means of compression and expansion of the cochlear walls is believed to play an important role. This alteration is the result of propagation of the longitudinal sound wave in the skull and consequent compression and expansion of the bone with this wave. Asymmetry in scala vestibuli and tympani, as well as in impedance of the oval and round window, results in fluid flow and excitation

of the basilar membrane (primarily in higher frequencies). Other factors are generally minor contributors to bone conduction hearing (with exceptions in anatomical variations), these are elaborately discussed by Stenfelt et al [2].

The mechanisms of vibration transmission from the skull bone to the cochlea are not only applicable to the ipsilateral cochlea, but additionally transcranial vibration transmission will result in stimulation of the contralateral cochlea. Especially in frequencies up to 1 kHz the transcranial attenuation is close to 0 dB, i.e. sound transmission to the contralateral cochlea is assumed to be (near) equal to that of the ipsilateral cochlea. For higher frequencies the transcranial transmission starts to decrease and the attenuation becomes +15 to +20dB at 10kHz [3]. This aspect of bone conduction hearing is important with application of bone conduction hearing implants, which will be discussed later on.

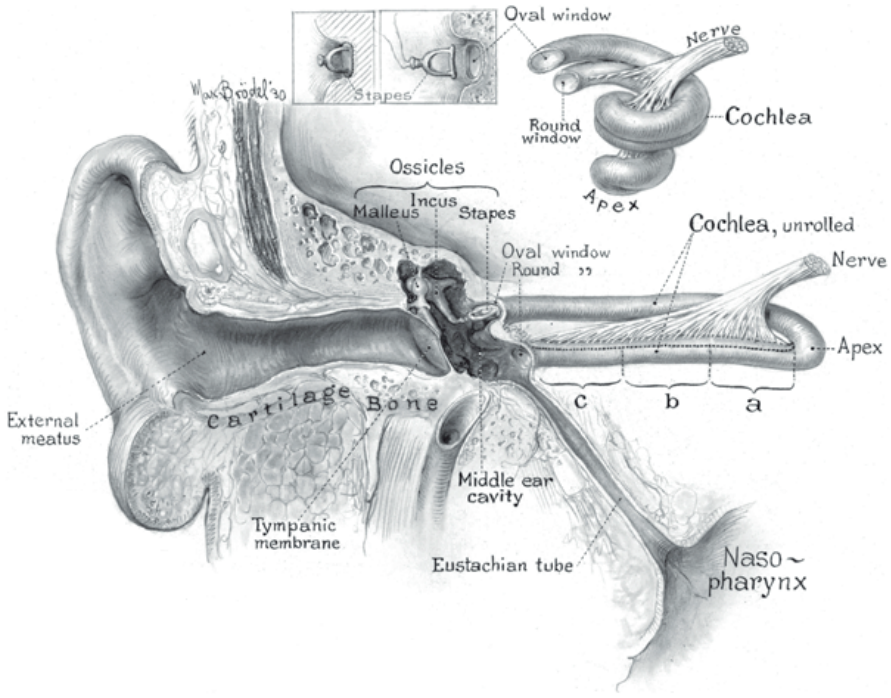
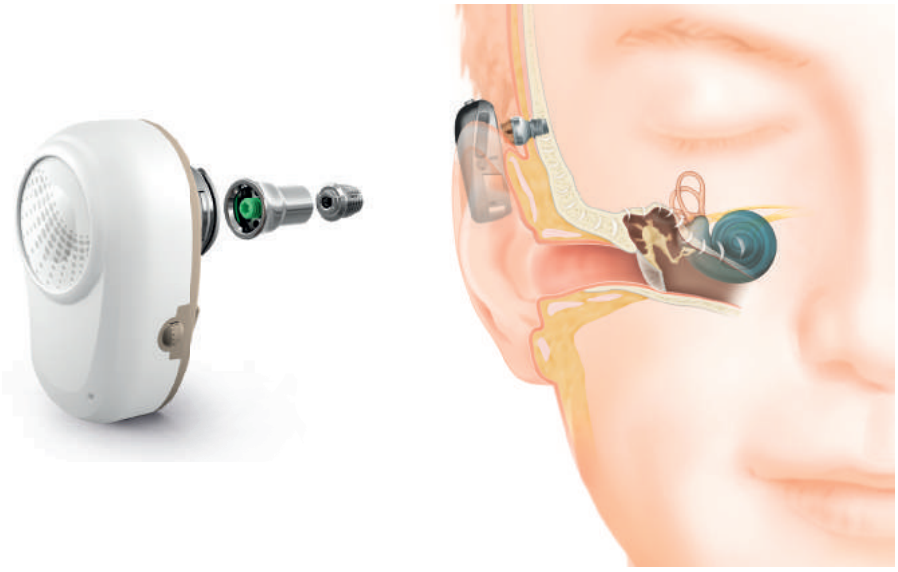


Figure 1. The ear and air conduction hearing
The cochlear duct is drawn as though unrolled from its original spiral shape. Segments 'c', 'b', and 'a' indicate high, to middle, to low frequency regions. Vestibular system not shown. Based on a figure from M. Brodel, 1930

Hearing loss

The previous paragraph described the physiology in air and bone conduction hearing. In normal hearing patients sound transmission is generally achieved by means of the more efficient air conduction hearing resulting from a sound wave captured by the auricle.



a. Image A shows the separate parts (image provided by Oticon Medical™. Reprinted with permission)

b. Image B shows the system as implanted (image provided by Cochlear™ BAS. Reprinted with permission)

Figure 2. The percutaneous bone conduction hearing implant.
The system consists of three parts; a titanium implant, an abutment and a sound processor or bone conduction device (BCD).

When, however, one of the contributing parts of the ear is abnormally developed or dysfunctioning, this will result in a hearing loss. Sensorineural hearing loss (SNHL) is the most common type of hearing loss, this is caused by any dysfunction or abnormality in the cochlea or auditory pathway to the brain and can often be rehabilitated by means of air conduction hearing aid. Conductive hearing loss (CHL) is caused by any developmental disorder or dysfunction of the external and/or middle ear. In these cases hearing is limited by an inefficient sound transmission and consequently diminished auditory input to the cochlea. Mixed hearing loss (MHL) is a combination of both conductive and sensorineural components. Furthermore, each type can either be congenital (present at birth) or acquired in onset and have various underlying causes. For some hearing problems medical or surgical interventions are available, while in other diagnosis rehabilitation options like hearing aids are preferable or sometimes the only option available. Bone conduction hearing implants are mainly applied for conductive or mixed hearing loss, either unilateral or bilateral. Especially for patients with external auditory canal and/or middle ear disorders, in which the use of a conventional air conduction hearing aid is contraindicated, not possible (atresia/microtia) or when reconstructive surgery is not a feasible option [4]. Furthermore, in unilateral sensorineural hearing loss the previously described transcranial transmission of vibrations to the contralateral functioning ear can be utilized for hearing aid fitting [5,6].

Bone conduction hearing implants

The classic percutaneous system, which is the standard device system in our clinic and main subject of this thesis, consists of three parts; a titanium implant, an abutment and a sound processor or bone conduction device (BCD) (Figure 2). Before the development of this system, bone conduction hearing solutions comprised a vibrator that was pressed against the skin at the mastoid, by a steel spring or headband. That bone conduction vibrator was connected to a body-level power processor. Later on, the bone conduction vibrator was supported by eyeglasses, where the microphone and amplifier where mounted in the arms of the spectacles [7-9]. These conventional bone conduction hearing aids were fitted successfully, and from the 1960s to the 1990s these were the most widely used bone conduction hearing devices. However, various problems remained, like dampening of sound by skin and subcutaneous tissue, pressure related skin problems and a variable position of the transducer. To overcome these problems, the idea to create a direct connection of the vibrator with the mastoid bone through a percutaneous implant was developed. The percutaneous bone conduction hearing implant was developed in 1977 at Gothenburg Sweden by a team led by Tjellström, Håkansson and Brånemark [10]; and is commercially available since 1987. The concept of using titanium implants for a rigid fixation between a titanium fixture and bone was derived from dental implantology, were these implants were used as a means of providing an anchor for dental prostheses [11]. The titanium implant is inserted in the temporal bone and a skin-penetrating abutment is attached to the implant to facilitate coupling of the BCD. The sound processor microphone captures the sounds and the sound processor with vibrator converts the sound pressure waves into mechanical vibrations that vibrate the mastoid bone through the titanium abutment and implant, stimulating the cochlea. As a result any problems in the outer of middle ear are bypassed in patients with conductive or mixed hearing loss [10]. In patients with single sided deafness, the vibrations are sent to the contralateral 'good' inner ear [12]. The percutaneous system is currently a well-established method and is considered the gold standard in bone conduction hearing in our clinic [4,13].

Advances in surgery, implants and sound processors

Since the introduction of the bone conduction hearing implant in 1977, many improvements have been made in the sound processors, implants and in the surgical procedure [14,15]. Amongst others, the introduction of digital and more powerful sound processors and wireless options has resulted in advances [16,17]. More recently, the introduction of wider and differently shaped implants for percutaneous systems, new surgical techniques and (re-introduction) transcutaneous systems have expanded the field [18]. Some of these new implants and surgical techniques are discussed in more detail in this thesis (Chapters 5-8).

The re-introduction of transcutaneous implants needs some extra explanation. As discussed previously, bone conduction hearing devices were originally introduced as transcutaneous solutions, positioned by a steel spring or mounted in eyeglasses. Due to more effective sound

transmission, the percutaneous coupling was adopted as a new standard. At approximately the same time as the percutaneous coupling, a magnetic transcutaneous BCD was introduced, the Xomed Audiant [19]. This system resulted in insufficient sound transmission and pressure related skin issues, which resulted in a withdrawal from the market soon after its introduction. In recent years however, a revival of transcutaneous applications has been observed. These systems are re-introduced with the intention to overcome some of the disadvantages or complications of percutaneous coupling (loss of the titanium implant, recurrent soft tissue problems around the abutment, and potential aesthetic issues related to the percutaneous abutment). The availability of new and more powerfull bone conduction processors have played an important factor in this revival. These transcutaneous applications yield a magnetic coupling over/through the skin; however, they can either be passive or active transcutaneous. In the passive transcutaneous systems the mechanical vibrations from the vibrator are transmitted through an intact skin to a passive subcutaneously placed magnet attached to the temporal bone (Sophono® [20] or Baha® Attract [21], the latter is discussed in Chapter 8, also see Figure 3). In active transcutaneous devices the vibrator is implanted under the skin and electromagnectic signals from the sound processor are transmitted through the intact skin (Bonebridge® [22], Sentio which was previously named Bone Conduction Implant [23] or OSIA, last two are not commercially available at the time of writing this thesis; Figure 3).

Another transcutaneous, non-surgical option, is the use of a bone conduction device on a softband. This softband option is frequently used in younger children bridging the period untill old enough for implantation as a more comfortable alternative to the metal headband and sometimes in a selection trial before implantation in adults [24]. This option obviously has a less efficient sound transmission compared to the percutaneous system, hence generally is not a definite rehabilitation option.

A more complete overview of different systems has been provided previously by Dun et al. [15] and more recently by Reinfeldt et al [18]. Furthermore, elaborate reviews can be found in prior Nijmegen theses about bone conduction devices [25-32].

Outline of this thesis

The aim of the first part of this thesis is the evaluation of various clinical outcomes of bone conduction hearing implants.

In chapter 2 the association between the occurrence of soft tissue reactions, revision surgeries and implant loss and several comorbidity factors is evaluated. This study was initiated based on previously identified other comorbidity risk factors and suggested pathophysiological mechanisms, as well as results in clinical practice. A large patient cohort of 581 patients with long-term follow-up was used to assess the association of several comorbidity factors.

A remarkable increase in soft tissue complications in the paediatric patients compared to the previous generation implants was the motive for initiation of the study described in

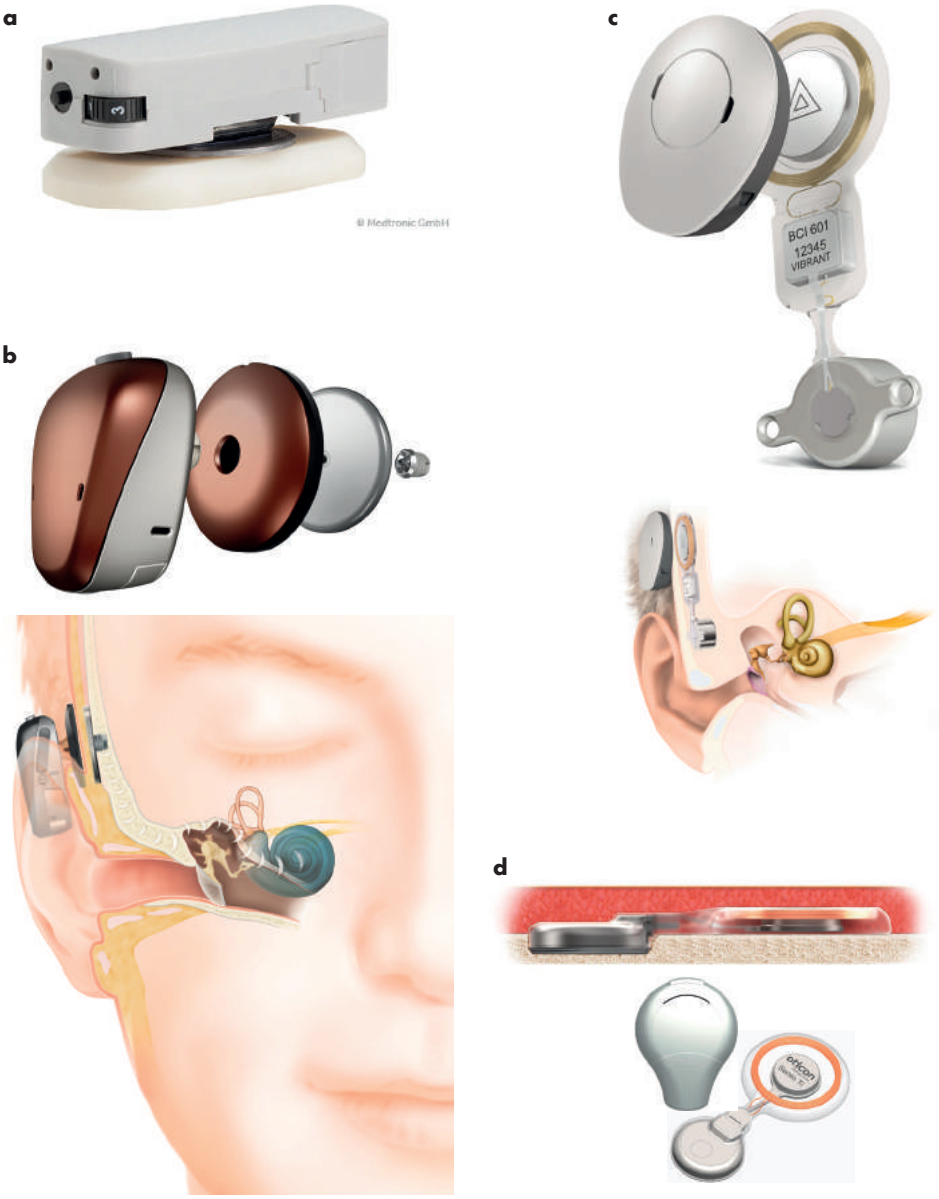


Figure 3. Transcutaneous bone conduction hearing implants
a. Sophono® Alpha 2 (Image provided by Medtronic™. Reprinted with permission)
b. Baha® Attract (Image provided by Cochlear™ BAS. Reprinted with permission)
c. Bonebridge ® (Image provided by MED-EL™. Reprinted with permission)
d. Sentio (Image provided by Oticon Medical™. Reprinted with permission)
The Sentio system is not yet commercially available
e. OSIA
The OSIA system is not yet commercially available, no images are available yet

chapter 3. This increase in complications was noticed from the time of introduction of a new type of implant, the Cochlear™ BI300 implant. This implant previously showed good results in adult patients, however, the results in the paediatric patient population were not yet reported in full. The rate of complications with this new implant was assessed in two tertiary referral centres.

Chapter 4 focuses on directional hearing. The results of a spatial discrimination and a sound localization test in children with a bilateral conductive hearing loss, who where rehabilitated with bilateral bone conduction devices, are discussed in this chapter. An added value of bilateral versus unilateral application was expected in this patient population based on previous studies. The current study served to provide more evidence on improved directional hearing and to provide a closer insight in these directional hearing abilities.

The second part of this thesis discusses the clinical effectiveness and safety of new implants and a new surgical technique. In chapter 5 the five-year follow-up of a post-market trial on a new type of implant type is described. This study compares the BI300 implant from Cochlear™ to the preceding (previous generation) flange fixture. The studied implant included a wider diameter implant and a differently shaped abutment, aimed to reduce soft tissue reactions and increase implant stability. The current study focuses on these outcomes at long-term (five year) follow-up.

Chapter 6 describes the results from a randomized controlled trial comparing two percutaneous implants from Oticon Medical™. The wide Ponto® implant (4.5mm diameter implant) was compared with the previous generation Ponto® implant (3.75mm diameter implant). This study focused on stability outcomes and implant survival, which were expected to improve with the new implant. Furthermore, soft-tissue outcomes and subjective benefit were evaluated.

In chapter 7 a new surgical technique for implantation of percutaneous bone conduction hearing implants is discussed. At the time of the study a simplified linear incision surgery, without a soft tissue reduction step, was recently introduced by another bone implant research centre (Hultcrantz et al, Karolinska University Hospital, Stockholm, Sweden). In order to further evaluate the results of this surgical technique, a study was conducted within our centre comparing the results of this new technique with the standard linear incision technique using the same type of bone conduction hearing implants (Ponto® wide from Oticon Medical™) in both groups.

Chapter 8 discusses the results of a post-market trial on a new transcutaneous implant system, the Baha® Attract from Cochlear™. This passive transcutaneous implant system was recently introduced and this was the first, and largest multicentre trial after it became commercially available. Patients with conductive/mixed hearing loss, as well as single-sided deafness patients, were included and evaluated on various clinical and audiological parameters.

All studies are discussed and summarized in chapter 9.

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Part I

Effectiveness and safety of implants in current practice

chapter 2

A retrospective cohort study on the influence of comorbidity on soft tissue reactions, revision surgery, and implant loss in bone-anchored hearing implants

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Otology & Neurotology 2015 Jun;36(5):812-8

Objective To identify risk factors for complications after bone anchored hearing implant (BAHI) surgery

Study design Retrospective cohort study

Setting Tertiary referral centre

Patients All adult patients who received titanium bone-anchored hearing implants at our clinic between September 1, 1988, and December 31, 2007, were approached to fill out a questionnaire on comorbidity factors. A total of 581 patients with 669 implants were included in the analysis.

Main outcome measures Implant loss, soft tissue reactions and revision surgery after BAHI implantation

Results Skin disease and profound learning difficulties were risk factors for time to first soft tissue reaction, hazard rate ratio of 3.41 (95% CI 1.45-8.01) and 3.42 (1.03-11.39) respectively. Female gender showed a trend toward a negative risk for time to first soft tissue reaction, hazard rate ratio 0.60 (0.35-1.03). In multivariable analysis skin disease and female gender were observed as independent associative factors, adjusted hazard ratio 3.08 (1.32-7.16) and 0.56 (0.33-0.94). For revision surgery, female gender and cardiovascular disease were identified as negative risk factors in univariable analysis and smoking showed a trend toward a negative risk, with hazard ratios of 0.15 (0.07-0.32), 0.07 (0.03-0.20) and 0.51 (0.24-1.07) respectively. In multivariable analysis smoking and female gender were observed as independent associative factors, adjusted hazard ratio 0.45 (0.22-0.95) and 0.14 (0.06-0.30). Smoking could be identified as a risk factor for implant loss with a hazard ratio of 3.32 (1.36-8.09).

Conclusions Retrospective analysis of comorbidity factors and clinical outcomes revealed risk factors for postoperative complications after BAHI surgery.

Introduction

The percutaneous bone anchored hearing implant (BAHI) was introduced in 1977 by Tjellström[1]. For more than 35 years, it has been used successfully as a treatment for patients with conductive or mixed hearing loss. The BAHI shows a high degree of safety and the success rate concerning audiometric outcomes and patient satisfaction is stable over time [2]. Nevertheless, complications are encountered during follow-up. The most frequent complications of the BAHI involve soft tissue reactions around the titanium skin-penetrating implant and implant loss[3-7].

The most commonly used classification for soft tissue reactions around percutaneous implants was proposed by Holgers et al. in 1988[3]. This classification describes five different degrees of soft tissue reactions. A reaction of Holgers grade 2 or higher is generally considered as an adverse reaction in need of treatment. Subsequently, these soft tissue reactions may result in more serious adverse outcomes, such as implant extrusion and chronic wound infection [5,6]. In a large series described by Dun et al. [4], a soft tissue reaction Holgers grade 2 or higher was recorded in 4.5% of all observations. Higher soft tissue reaction scores were seen in children and patients with profound learning difficulties. As for comorbidity factors, some studies [8-10] identified a relationship between obesity and soft tissue complications at the implant site. The influence of other comorbidity factors on soft tissue reaction in BAHI implantation has been analysed in a study by Zeitler et al [11]. This study describes an increased risk of skin-site complications for African American patients, but for the other predisposing factors (tobacco use, diabetes mellitus, immunosuppression) no relation could be found in this relatively small series. In other medical fields where comparable titanium implants are used for even a longer period of time, especially the field of dental implantology, larger retrospective studies show that diabetes mellitus and a history of cardiovascular disease are significant risk factors for peri-implant disease [12,13]. Furthermore, dermatologic diseases such as eczema and psoriasis might influence soft tissue reactions post BAHI surgery. Two BAHI studies report a high number of patients with skin disease in those presenting with an adverse skin reaction [14,15]. Most studies on complications after BAHI surgery merely mention possible influence of comorbidity factors on soft tissue reaction in a descriptive manner, with no further analysis.

A more serious complication, also likely to be affected by comorbidity, is implant loss. Reported frequency of implant loss varies from 3% to 27% in adult patients [4,5,7,16]. Few articles have been published on risk factors for implant loss. Previous irradiation of the implant site is shown to be a risk factor for implant failure [17]. Furthermore, Horstink et al. [18] showed a significantly higher rate of implant loss in Type 2 diabetes mellitus (DM2) patients compared to non DM patients. Impact of other comorbidity factors on implant loss is not yet identified. However, conditions that influence bone remodelling might affect the

process of osseointegration around a BAHI. Numerous potential local and systemic factors are mentioned in various studies; however, definite evidence is often lacking.

The aim of the current retrospective cohort study was to identify the influence of comorbidity on soft tissue reaction, revision surgery and implant loss in a large population of patients with the same type of BAHI. Studies on wound healing in general have led to the hypothesis that among patients with relevant comorbidities, peri-implant complications might be higher compared with healthy adult patients. Knowledge of these potential risk factors could be useful in patient counselling, selection of surgical procedure, and postoperative surgical site care. We retrospectively analysed a consecutive series of more than 1000 implants on clinical outcomes, with emphasis on adverse events and potential risk factors. The same series was previously analysed by Dun et al. [4], focusing on age differences and loading time, and by Horstink et al. [18], focusing on the effect of diabetes mellitus on implant loss. For the current study, the available data were re-analysed and combined with additional topics focusing on these extended clinical research questions.

Material and methods

Participants

All patients who received titanium bone-anchored hearing implants at our clinic between September 1, 1988, and December 31, 2007, were identified. This resulted in a cohort of 974 patients with 1150 implants. During follow-up, 140 patients passed away. All other patients were asked to fill out a questionnaire. Patients were contacted by mail and after not responding the first time, two more attempts were made to contact these patients by mail or telephone. One hundred and eighty-seven patients were unable to be contacted during follow-up or did not want to participate in this study. This resulted in a total of 647 patients who were eligible for inclusion in the analysis of this retrospective cohort study, of which only the adult patients (aged 18 or older) were included in the definitive analysis (n=581).

Surgical techniques and post-surgery protocol

The original Tjellström skin graft technique [19] was used from 1988 until 1995, after which the Nijmegen linear incision technique with tissue reduction was implemented [14,20]. After implementation this was the only technique used. Only one type of implant was used (as-machined Baha flange fixture, Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden). The frequency of postoperative visits to the outpatient clinic varied from once every four months in the first years after BAHI surgery, to once a year, which is the current standard. During all follow-up visits, a standardised checklist was used, which included registration of soft tissue reaction according to the Holgers grading system.

Questionnaire and case analysis

The questionnaire was composed of 11 questions. Patients were asked if they were still using the bone conduction device and if they had ever been diagnosed with skin disease, hypertension, cardiovascular disease, or other comorbidity factors (not further specified; thyroid disease was mentioned as an example), including the year of diagnosis. For the patients with missing information on the year of diagnosis, medical files were searched and the database was completed with this missing information. Only diagnoses made before or in the year of operation were taken for further analysis. An exception was made for DM2, where a separate analysis was conducted for patients diagnosed during follow-up, as was also carried out in our previous analysis on largely the same series[18]. Reanalysis of the effects of DM2 was included in the current study, as the current study emphasises on the relation between DM2 and soft tissue reactions and revision surgery. In addition, a longer period of follow-up was available for implant loss, until January 2013.

Furthermore, patients were asked for their height and weight, smoking and alcohol intake status, and any changes in these factors since BAHI surgery. Smoking was handled as either active or non-smoker, and when patients stated they had quit smoking the year before BAHI surgery, they were counted as non-smokers. For alcohol, drinking two or more units daily reported in the questionnaire was included as a risk factor. Body Mass Index (BMI) was calculated for all patients, and changes reported since surgery were included in this calculation. In addition, data concerning age at implantation, gender, profound learning difficulties, soft tissue reactions, revision surgery and implant failure were collected from patients' medical charts and our BAHI database. A soft tissue reaction grade 2 or higher was interpreted as an adverse soft tissue reaction.

For baseline characteristics time and age of first implantation, as well as comorbidity status at first implantation are presented.

Statistical analysis

The influence of risk factors on time to implant loss, first soft tissue reaction and time to revision was analysed with a proportional hazards regression model to obtain hazard rate ratios.

Because of multiple implants per patient (up to 5 implants) each patient can potentially experience several events. When no event was observed during observation time of an implant the time-to-event was censored at the time of implant loss or, for the last implant, the end-of-study date. This censoring mechanism was applied to all three time-to-event analyses.

To take into account the dependency of the observations a random effects proportional hazards model with Weibull baseline hazard was performed for the time-to-event data. A normal distributed frailty was incorporated for each individual. We assumed independent data within an individual.

The influence of risk factors on the number of tissue reactions during observation time of an implant was analysed with a normal random effects Poisson regression model. Again incorporation of a random effect for each individual accounted for the dependency structure of the data. The logarithm of the observation time was used as offset.

Because previous analyses identified a significantly higher implant loss and soft tissue reactions in children, influence of comorbidity factors was only studied in adult patients (over the age of 18 years).

For each time-to-event analysis potential risk factors (P<0.10) in univariable analysis were incorporated in a multivariable regression model. All analyses were performed using SAS software version 9.2.

Results

Participants

The adult study population consisted of 581 patients with a total of 669 implants. A total of 65 patients were implanted bilaterally. The median age at first implantation was 52 years (interquartile range 42-60 years), 54% of patients were female. The prevalence of skin disease was 8.3%. Approximately 30% of patients were active smokers at time of surgery and 19.7% had a type of cardiovascular disease. Frequency of DM2 at time of surgery was 5.4%; during entire follow-up it was 11.2%. Total follow-up time for all patients was 7120 person-years, median implant time per patient was 10.9 years. All baseline characteristics are shown in Table 1.

Soft Tissue Reaction

A Holgers grade 2 soft tissue reaction or higher was noticed at least once in 123 implants (18.4%). Over 40% of these adverse soft tissue reactions per implant were noticed in the first year after surgery.

Skin disease could be identified as a new risk factor for the time to first adverse soft tissue reaction, with a hazard rate ratio of 3.41 (95% CI 1.45-8.01, p=0.005). The presence of profound learning difficulties resulted in a hazard ratio of 3.42 (95% CI 1.03-11.39, p=0.045) for time to first adverse soft tissue reactions, female gender resulted in a hazard rate ratio of 0.60 (95% CI 0.35-1.03, p=0.062). The unadjusted hazard ratios for all risk factors with 95% confidence intervals are shown in table 2 and graphically displayed in figure 1.

When including comorbidity factors with a p-value of < 0.10 in a multivariable model, the hazard ratios only changed marginally. For gender, the hazard ratio was 0.56 (95% CI 0.33-0.94; p=0.029), for skin disease 3.08 (95% CI 1.32-7.16; p=0.009) and for profound learning difficulties 2.89 (95% CI 0.88-9.55; p=0.081).

Table 1. Baseline characteristics

		N	%
Total patients		581	100%
Total implants		669	100%
Time	**1988-1994**	60	10,3%
	1995-2001	206	35.5%
	2002-2007	315	54.2%
Gender	**Male**	268	46.1%
	Female	313	53.9%
BMI	**>30**	80	13.8%
DM 2	**DM2**	31	5.4%
	DM2+ prediabetes	65	11.2%
Skin disease	**Eczema**	33	5.7%
	Psoriasis	15	2.6%
	Total	48	8.3%
Cardiovascular disease	**Hypertension**	86	14.9%
	Total	114	19.7%
Thyroid disease	**Yes**	37	6.4%
Profound learning difficulties	**Yes**	23	4.0%
Smoking status	**Active time surgery**	189	32.5%
Alcohol status	**More than 2 daily time surgery**	78	13.4%

The influence of risk factors on the number of adverse soft tissue reactions during observation time of an implant was also analysed. The estimated mean number of adverse soft tissue reactions was 0.027 per year. Skin disease induced an incidence rate ratio of 1.98 (95% CI 1.05-3.72, p=0.034). The unadjusted hazard ratios for all risk factors with 95% confidence intervals are shown in table 2 and graphically displayed in figure 2.

Revision surgery: soft tissue revision & abutment replacements

During the complete follow-up, in 79 of 669 implants, one or multiple revisions were performed (11.8%). Of these, 41 included soft tissue revision, 32 a higher abutment and 6 both procedures. Female gender and cardiovascular disease were identified as new negative risk factors and for smoking a trend toward a negative risk was seen, respectively hazard rate ratios of 0.15, 0.07 and 0.51. The unadjusted hazard ratios for all comorbidity factors with 95% confidence intervals are shown in table 2 and graphically displayed in figure 3.

When including comorbidity factors with a p-value of < 0.10 in a multivariable model, virtually the same hazard ratios were seen, except for cardiovascular disease. For female gender, the hazard ratio was 0.14 (95% CI 0.06-0.30; p<0.001), for cardiovascular disease 0.95 (95% CI 0.41-2.18; p=0.897) and for smoking 0.45 (95% CI 0.22-0.95; p=0.036).

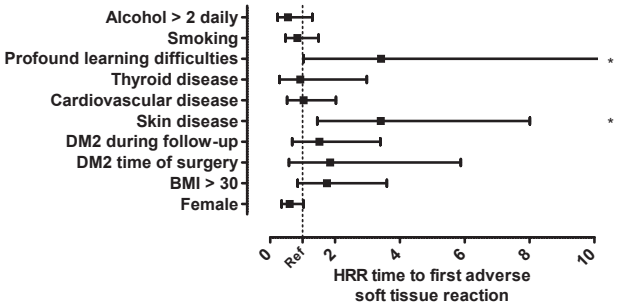

Figure 1. Influence of comorbidity factors on time to first adverse soft tissue reaction (Holgers score ≥ 2). Hazard rate ratio ± 95% CI. Random effects proportional hazards model: *p<0.05. Ref = Reference category.

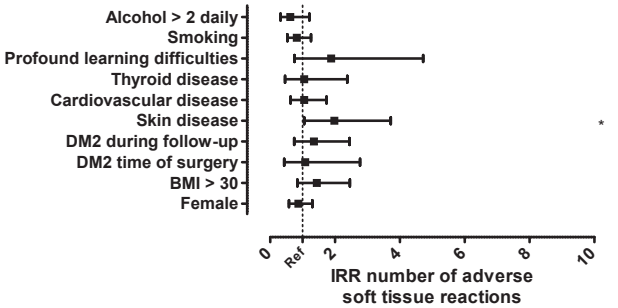

Figure 2. Influence of comorbidity factors on the number of adverse soft tissue reactions during observation time of implants (Holgers score ≥ 2). Hazard rate ratio ± 95% CI. normal random effects Poisson regression model: *p<0.05. Ref = Reference category.

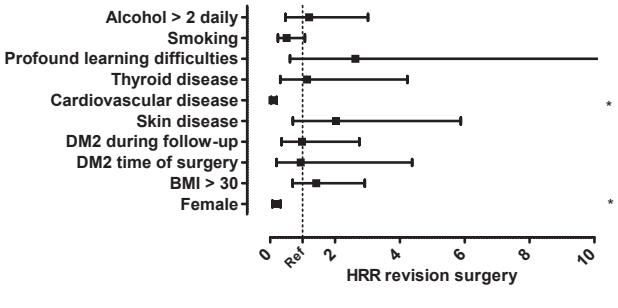

Figure 3. Influence of comorbidity factors on revision surgery (soft tissue revision and/or abutment replacement). Hazard rate ratio ± 95% CI. Random effects proportional hazards model: *p<0.05. Ref = Reference category.

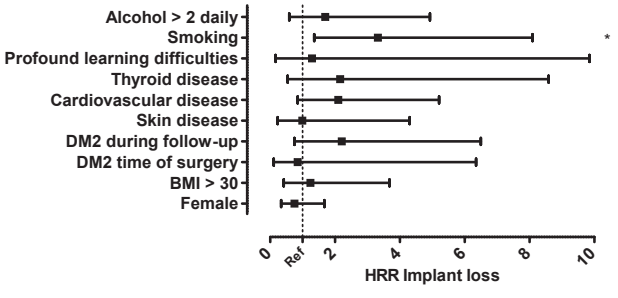

Figure 4. Influence of comorbidity factors on implant loss. Hazard rate ratio ± 95% CI. Random effects proportional hazards model: *p<0.05. Ref = Reference category.

Table 2. Influence of comorbidity factors

		First adverse soft tissue reaction			Number of adverse soft tissue reactions			Revision (revision surgery and/or abutment replacement)			Implant loss		
		HRR	**95% CI**	**P-value**	**IRR**	**95% CI**	**P-value**	**HRR**	**95% CI**	**P-value**	**HRR**	**95% CI**	**P-value**
Gender	**male**	Ref			Ref			Ref			Ref		
	female	0.60	0.35-1.03	0.062	0.87	0.58-1.30	0.50	0.15	0.07-0.32	<0.001	0.75	0.34-1.67	0.48
BMI	**<30**	Ref			Ref			Ref			Ref		
	>30	1.75	0.85-3.60	0.12	1.44	0.84-2.46	0.18	1.42	0.69-2.92	0.33	1.24	0.42-3.68	0.70
DM2 time of surgery	**N**	Ref			Ref			Ref			Ref		
	Y	1.85	0.58-5.88	0.29	1.08	0.43-2.77	0.86	0.94	0.20-4.38	0.93	0.85	0.11-6.35	0.87
DM2 during follow-up	**N**	Ref			Ref			Ref			Ref		
	Y	1.52	0.68-3.40	0.30	1.35	0.74-2.45	0.32	0.98	0.35-2.75	0.96	2.21	0.75-6.50	0.14
Skin disease	**N**	Ref			Ref			Ref			Ref		
	Y	3.41	1.45-8.01	0.005	1.98	1.05-3.72	0.034	2.03	0.70-5.88	0.19	0.99	0.23-4.30	0.99
Cardiovascular disease	**N**	Ref			Ref			Ref			Ref		
	Y	1.03	0.52-2.03	0.93	1.05	0.63-1.74	0.86	0.07	0.03-0.20	<0.001	2.10	0.85-5.21	0.10
Thyroid disease	**N**	Ref			Ref			Ref			Ref		
	Y	0.93	0.29-2.98	0.89	1.05	0.46-2.38	0.91	1.14	0.31-4.23	0.84	2.16	0.54-8.59	0.27
Profound learning difficulties	**N**	Ref			Ref			Ref			Ref		
	Y	3.42	1.03-11.39	0.045	1.88	0.75-4.72	0.17	2.63	0.61-11.26	0.19	1.29	0.17-9.85	0.80
Smoking	**N**	Ref			Ref			Ref			Ref		
	Y	0.84	0.47-1.49	0.55	0.82	0.53-1.26	0.36	0.51	0.24-1.07	0.074	3.32	1.36-8.09	0.009
Alcohol	**<2 daily**	Ref			Ref			Ref			Ref		
	> 2 daily	0.55	0.23-1.30	0.17	0.62	0.32-1.21	0.16	1.20	0.47-3.02	0.70	1.7	0.59-4.93	0.32

IRR = incidence rate ratio, Ref = reference category, HRR = Hazard rate ratio

Implant Loss

During complete follow-up, 50 of the 669 implants were lost (7.5%). In the first year after surgery, 11 implants were lost (22%). 29 of the 50 implant losses (58%) occurred in first five years. Smoking was the only risk factor that could be identified in univariable analysis, hazard rate ratio 3.32 (95% CI 1.36-8.09, p=0.009). A trend for higher implant loss was seen in patients with cardiovascular disease (HRR 2.10) and when during follow-up DM2 was present (HRR 2.21). The unadjusted hazard ratios for all risk factors with 95% confidence intervals are shown in table 2 and graphically displayed in figure 4.

Discussion

Principal findings

In the current study, clinical outcomes of 581 patients with 669 implants were studied with a total follow-up time of 7120 person-years, implant loss was observed in 7.5% of implants and adverse soft tissue reactions in 18.4% of implants. For adverse soft tissue reactions, skin disease could be identified as a risk factor. Smoking was a risk factor for implant loss. In addition, fewer revisions were seen in the female gender and cardiovascular disease group in univariable analysis; in multivariable analysis female gender and smoking were identified as negative risk factors for revision surgery.

Comparison with other studies

Evaluation of clinical outcomes of BAHI surgery has been extensively reported on since its introduction. Over the past years, several risk factors were evaluated, mostly in small populations and with short follow-up, as briefly reviewed in the introduction of this manuscript. Younger age, profound learning difficulties, obesity, tobacco use, diabetes mellitus, cardiovascular disease, ethnic background, and skin disease have all been discussed [4,14,15,21-23]. In the current study, our entire BAHI database was evaluated for all these factors combined. Moreover, evaluation was done not only with respect to implant loss but also referring to revision surgery and soft tissue reactions, being more difficult outcome parameters to interpret. The current study is one of the largest series to date studying risk factors for these parameters. Some risk factors reported elsewhere can be confirmed by this study, such as skin disease and smoking. The negative effect of smoking on implant survival was already reported in numerous dental implant studies [22,24,25]. For dermatologic diseases such as eczema and psoriasis the skin barrier function and immune response are negatively affected, and a higher bacterial colonization of the skin is found in several studies [26-29], which could possibly explain the higher soft tissue complication rate. However, other risk factors previously described could not be confirmed. As stated in the introduction, Berenholtz et al. [8], Rebol [9] and Kraai et al. [10] identified high BMI as a risk factor for soft

tissue problems, explained by the relation between body mass index and retroauricular subcutaneous tissue thickness [30]. Such a significant relation between BMI and soft tissue reactions could not be identified in this series; only a trend towards higher incidence was noticed in our series. Prevalence of BMI ≥ 30 was 30% in the series by Berenholtz et al., compared to 14% in the current study. This difference in patient group might explain the fact that this risk factor was not confirmed in the current study. Notable are the outcomes of the current study on diabetes mellitus and implant loss. DM was not seen as a risk factor in the current study, merely a trend was noticed. This can be seen as contradicting a previous analysis by Horstink et al [18], especially since it is the same patient dataset. However, the reduced study group due to methodological constraints, longer follow-up and different statistical analysis can explain this discrepancy.

Strengths and limitations

The current study has several strengths. First of all, the size and duration of follow-up of the analysed patient group lend for more robust conclusions. Moreover, homogeneous exposure was achieved since only one implant type was used and in the majority of patients the same surgical technique was applied. Additionally, over 95% of operations were performed by 3 surgeons (CC, EM, DK), so it was expected that the learning curve was relatively short and when comparing three time periods (1988-1994, 1995-2001, 2002-2007) no major differences were noticed in the complication rate, albeit not formally analysed. Lastly, there was a high response rate with nearly 70% of all our patients filling out the questionnaire and thus could be included in the analysis.

Selection bias in the selected patient group for analysis was considered to be minor. Reported incidences of, for instance, smoking and alcohol are comparable to numbers in the total Dutch population [31]. Moreover, clinical outcomes were comparable to what was seen in previous report on the entire patient group [4]. The somewhat higher incidence of implant loss and revisions in the current study can be considered to be due to longer follow-up. With a similar follow-up, the selected patient group (including patients < 18 years of age) results in an implant loss of 8.1% of all implants compared to the 8.3% found in the study by Dun et al [4].

Confounding effects of age on all clinical outcomes were corrected for in univariable analysis by excluding patients <18 years of age. Distribution of gender in cardiovascular disease groups was equal; however, in multivariable analysis smoking was identified as a confounding factor in the relation between cardiovascular disease and revisions. A higher number of patients with skin disease, 19.2% versus 8.1%, was seen in the patient group with profound learning difficulties versus no profound learning difficulties. However, in multivariable analysis on time to first soft tissue reactions, hazard ratios of skin disease and profound learning difficulties were approximately the same as in univariable approach.

To obtain information and identify potential risk factors in such a large group, a retrospective design was selected for the study. Obviously this design has some inherent limitations. A questionnaire was used in which patients were asked to report information on diagnosis made in the past, consequently, the data might include some inaccuracies as a result of this strategy. Potential information bias due to measurement errors in recall of comorbidity factors are expected to result in an underestimation of associations between comorbidity factors and complications. All missing information in the questionnaires was completed by a search of patient charts. Nevertheless, this design still depends on proper clinical documentation and an appropriate follow-up. Follow-up protocol in our centre adheres to strict guidelines; visits are planned at 1 week, 3 weeks and after this yearly. During all visits, a Holgers score is noted, whereby an appropriate follow-up is guaranteed.

Conclusion

In conclusion, several risk factors for adverse events following BAHI implantation could be identified in the current retrospective cohort analysis. For soft tissue reactions the effect of skin diseases was newly identified and negative risk factors for revision surgery were recognized. Furthermore, smoking was identified as a risk factor for implant loss. These factors should be included in patient counselling and selection of surgical and postoperative procedures. Moreover the current results could be seen as a reference for upcoming (long-term) clinical results of new implants and advances in surgical technique, like the tissue preservation technique. Developments and expected improvements in bone anchored hearing implants, abutments and concomitant surgical technique can be compared to the current results. The current study adds important data to what is available to date, as it is the first large series analysis on comorbidity risk factors in BAHI surgery.

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chapter 3

Clinical results of Cochlear™ BIA300 in children: experience in two tertiary referral centres

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Objectives To evaluate clinical outcomes of the Cochlear™ BIA300 in the pediatric population.

Study design Historical cohort study

Setting Two tertiary referral centers

Patients All patients implanted with the BIA300 from November 2011 to January 2014 and 17 years or younger during surgery were included in this cohort study.

Main outcome measures Number of soft tissue reaction scores according to Holgers, local and systemic treatment of soft tissue reactions, revision surgeries and implant loss.

Results Since introduction of the BIA300, 79 children have been implanted in both centers. During the mean follow-up of 11.7 months per implant, 15.7% of 115 implants received at least two local treatments for peri-abutment soft tissue reactions. Moreover, in 32 implants an adverse soft tissue reaction (Holgers 2 or higher) was noted at least once. In 28.7% of implants one or multiple revision surgeries were required. Implant loss occurred in 4 patients (3.5% of all implants), additionally, in five children the abutment had to be removed because of persistent soft tissue problems.

Conclusions The current study confirms good implant survival for these implants in pediatric patients. The number of adverse soft tissue reactions found in the current study resembles numbers reported on previous generation implants and abutments in children. However, for revision surgery (soft tissue revision and/or abutment change), an increase in frequency is noticed compared to reported results on previous generation implants and abutments, whether this is the result of the new implant or other factors cannot be concluded on the current series. The total aspect of the presented data are of importance in the decision making for a specific type of percutaneous bone anchored hearing implant.

Introduction

The first clinical report on titanium implants in the temporal bone for anchorage of hearing devices dates back to 1981 [1]. This article reports on a two-staged surgical technique in unilaterally implanted, adult patients. During the follow-up of 26-46 months no major soft tissue complications or implant losses were reported in this article. Over the past few decades indications for bone anchored hearing implants (BAHIs) have extended, younger patients are now being implanted and new surgical techniques and implants have become available. More than ever, in recent years new bone conduction devices and several types of implants and abutments have been developed rapidly. One of the new implant systems, the Cochlear™ BIA300, became commercially available in 2010. By then, the first clinical trial with this implant in adult patients was already conducted and soon after reported on [2]. The six-month report showed higher mean Implant Stability Quotient (ISQ) values and less soft tissue reactions for the new, wider implant compared to the previous generation implant. The good outcomes could be confirmed in other studies [3-5] and in long term follow up [6], and resulted in a complete substitution of the previous generation implant in all new BAHI surgeries, not only in adult patients but also in the pediatric population. During the last few years, however, in both centers, we noticed a high incidence of soft tissue reactions, revision surgery and non-users in our pediatric BAHI population. It is important to emphasize that the first report on this novel BIA300 [2], like the first clinical report [1], just included adult patients. This is the case in most studies reporting on clinical outcomes, since children are usually not included in clinical trials and smaller numbers of patients are available. However, clinical outcome evaluation in children is highly relevant, as previous series showed a significantly higher incidence of complications in children compared to adults (implant loss approximately 15%), all implanted with the previous generation implants [7]. The aim of the current study was to verify the subjective increase of soft tissue problems in our pediatric BAHI population. We reviewed the results of soft tissue complications and implant survival in our pediatric patients implanted with this specific implant.

Methods

Patients

All patients implanted with the Cochlear™ BIA300 between November 2011 and January 2014, and 17 years or younger during surgery were selected from our BAHI database and included in this historical cohort study. Patients with previous bone conduction hearing implant surgery on the same side were excluded. A minimum of 1 postoperative visit after abutment insertion (i.e. second stage surgery) had to be available. The records for this study spanned a 3-year period, November 2011 till October 2014. Since all medical

charts were reviewed at the end of this period, surgeries were at least 10 months before the final verification.

Surgical and postoperative procedures

Patients underwent a two-staged procedure under general anesthesia when younger than 10 years of age; when major craniofacial abnormalities were present; or other reasons for osseointegration problems were anticipated. In general, time between these two stages was 12 weeks. All other patients underwent a single-staged procedure with direct placement of the abutment. In Nijmegen the linear incision technique with tissue reduction was used. In Birmingham, additionally both the U-shaped and dermatome incisions were performed. All children had their first postoperative visit a week after surgery. During this visit the healing cap and the gauze with antibiotic ointment was removed, inspection of the incision was performed and it was standard care to start local cream (steroid-antibiotic cream). This was followed by an appointment for sound processor fitting after 6-12 weeks in case of single stage surgery, and after wound healing in case of two-staged surgery (varying from 1 to 4 weeks). Further follow-up protocol was as follows: Birmingham: 3, 6, 9, 12 months, followed by yearly visits; Nijmegen: 3, 9, 12 months, followed by yearly visits. If needed, appointments tailored to the individual clinical needs of the patients were available. At each visit, the degree of soft tissue reaction according to Holgers [8], or a description of soft tissue reactions and medical treatment were noted.

Case analysis

Data regarding patient demographics, indication for BAHI, comorbidity, surgical procedures and postoperative complications were collected from patients' medical charts. Age of implantation was defined as the patient age at the time of insertion of the abutment, i.e. age at second stage in case of two-staged surgery or age at single stage surgery. For patients with bilateral and sequential implantations the age at first implantation was taken. End of follow-up was defined as last visit to the ENT outpatient clinic within the indicated time frame. Main outcome parameters included soft tissue reactions classified with the Holgers grading system [8]; treatment given for adverse soft tissue reactions (excluding during the first two weeks after surgery, since this was standard care); revision surgery, i.e. soft tissue revision or abutment change, for soft tissue overgrowth; and implant loss. The Holgers' soft grading system is scored on a 5-point scale: 0, no signs of soft tissue reaction; 1, mild inflammation with slight redness; 2, moderate inflammation with redness and slightly moist skin; 3, redness, moist skin and granulation tissue; 4, an infection for which removal of implant and/or abutment is needed. Holgers 2, 3 and 4 skin reactions are classified as adverse soft tissue reactions.

Statistical analysis

All data was analyzed using Descriptive Statistics in the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp), version 20.0. For continuous variables means, standard deviations and ranges are reported; for dichotomous variables frequencies are reported.

Results

Baseline characteristics

Since introduction of the BIA300, 79 patients younger than 18 years have been implanted; 27 in Nijmegen and 52 in Birmingham. In Nijmegen 10 patients and in Birmingham 26 patients were implanted bilaterally. Except for one patient, all bilateral implantations were performed simultaneously. Mean follow-up per implant was 11.7 months (SD 7.7; range 0.2-30.2). A difference in follow-up time between centers was noticed; for Birmingham mean follow-up was 8.7 months per implant (SD 5.1; range 0.2 – 19.6) and for Nijmegen 17.9 months per implant (SD 8.6; range 3.7 – 30.2). Mean age at surgery was 9 years and 4 months. In 39 patients a congenital syndrome was present. Nine patients presented with childhood obesity. Other comorbidity factors were present in 27 patients; 6 with skin disease, 2 with diabetes mellitus, and 23 with a cardiopulmonary medical history. Cardiopulmonary history ranged from well-controlled asthma to severe cardiac abnormalities or obstructive airway problems for which surgery was indicated. In most patients, 50 of 79, etiology of hearing loss was defined as congenital.

All patient characteristics and its division per center are shown in Table 1.

Surgery characteristics

A total of 115 implants were placed, from these, 22 implants were placed during a single stage procedure. In 62 implantations a linear incision was used, in 44 a u-shaped incision and in 9 implants a dermatome approach was selected. Soft tissue reduction was performed in all but 35 cases. In most of the 115 implants, a 3mm BI300 implant (n=63) and a 6 mm BA300 abutment (n=85) was placed at initial surgery.

All surgery characteristics and its division per center are shown in Table 2.

Soft tissue reactions

In 76 implants, soft tissue scores according to Holgers grading system were recorded at least once. Of these implants, 32 presented with an adverse soft tissue reaction (Holgers 2 or higher) at least once (43.6% of implants with a Holgers notation, 27.8% of all implants). Out of a total of 290 Holgers observations, 55 were grade 2 or higher (18.9%). Highest Holgers noted in the entire group was Holgers grade 4 (2 implants). Of total of 55 implants

Table 1. Patient characteristics

		Birmingham		Nijmegen	
		Nr patients	%	Nr patients	%
Total patients		52	100%	27	100%
Sex	**Male**	30	57.7%	14	51.9%
	Female	22	42.3%	13	48.1%
Age at surgery	**Mean (SD), years**	9.5 (3.9)		8.9 (3.7)	
	Range	4.3 – 16.5		3.8 – 17.3	
Syndrome	**Total**	29	55.8%	10	37.0%
	Down	7	13.5%	0	
	Goldenhar/hemifacial microsomia	5	9.6%	3	11.1%
	CHARGE	5	9.6%	1	3.7%
	DeGrouchy	1	1.9%	2	7.4%
Comorbidity factors	**Skin disease**	4	7.7%	2	7.4%
	Diabetes mellitus	0		2	7.4%
	Childhood obesity	8	15.4%	1	3.7%
	Cardiopulmonary disease	19	36.5%	4	14.8%
Type of hearing loss	**Congenital**	29	55.8%	21	77.8%
	Acquired	23	44.2%	6	22.2%
Etiology of hearing loss	**Congenital aural atresia / microtia**	20	38.5%	17	64%
	Chronic otitis media	23	44.2%	5	18.5%
	Unilateral profound hearing loss, (all congenital)	7	13.5%	4	14.8%
	Congenital middle ear malformation	2	3.8%	1	3.7%

(47.8%) received at least one local treatment for a soft tissue reaction, of these, 18 implants (15.7%) were treated with local care at least twice. Local treatment regimens included a cream applied around the abutment (predominantly an antibiotic and/or steroid cream), silver nitrate cautery, or placement of a healing cap and gauze with antibiotic ointment. Systemic antibiotics were given to 14 patients in the total group, in one patient a total of three successive regimens were needed.

Results on soft tissue reactions for both centers are shown in more detail in Table 3.

Revision surgery

In total, 33 implants (28.7% of all 115 implants) needed revision surgery, i.e. an abutment change, soft tissue revision or both combined in one or multiple settings. A total of 4 implants required only soft tissue revision (3.5%), 9 implants required only an abutment

Table 2. Surgery characteristics

		Birmingham		Nijmegen	
		Nr implants	**%**	**Nr implants**	**%**
Total implants		78	100%	37	100%
Stages	**Single stage**	14	17.9%	8	21.6%
	2-staged	64	82.1%	29	78.4%
Surgical technique	**Linear incision**	25	32.1%	37	100%
	U-shaped	44	56.4%	0	
	Dermatome	9	11.5%	0	
Soft tissue reduction	**Yes**	45	57.7%	35	94.6%
	No	24	30.8%	2	5.4%
	Dermatome	9	11.5%	0	
Implant	**3mm**	33	42.3%	30	81.1%
	4mm	45	57.7%	7	18.9%
Abutment length at first implantation	**6mm**	49	62.8%	36	97.3%
	9mm	29	37.2%	1	2.7%

change (7.8%) and 20 implants required both soft tissue revision and an abutment change (17.4%). Out of the total of 29 abutment changes (25.2%), a new abutment was placed because of soft tissue problems (n=27) or abutment loss (n=2), with a longer abutment in 26 cases. In 27 implants, one revision was conducted, for four implants a second revision was needed and two implants required three revisions. Time to first revision was mean 7.9 months (SD 6.1; range 1.2-21.9). In 16 patients one revision under general anesthesia was required (including 5 bilateral revisions in one setting), three patients required two revisions under general anesthesia and one patient needed revision under general anesthesia three times.

Results on revision surgery for both centers are shown in more detail in Table 3.

During the last few years we noticed a preference for longer abutment placement and performing the initial surgery without soft tissue reduction (i.e. tissue preservation) in one of the two centers. When comparing the results on revision surgeries in Birmingham between the different surgical strategies, there seems to be better results for the patients with longer abutments and/or tissue preservation during initial surgery. Less soft tissue revisions are noticed after soft tissue preservation; furthermore, both soft tissue revision and abutment change are less frequent after placement of the 9mm abutment during initial surgery. However, some (minor) differences in patient characteristics are also noted between these groups, for example more children with a positive cardiopulmonary history in the soft tissue reduction group.

Results of revision surgery in different initial surgical strategies are shown in Table 4.

Table 3. Soft tissue outcomes

		Birmingham		Nijmegen	
	Nr of events	**Nr implants**	**Percentage of total implants Birmingham (percentage of implants with Holgers notations)**	**Nr implants**	**Percentage of total implants Nijmegen (percentage of implants with Holgers notations)**
Number of adverse soft tissue reactions	**0**	17	21.8% (42.5%)	27	72.9% (75%)
	1	13	16.7% (32.5%)	7	18.9% (19.4%)
	2	6	7.7% (15%)	2	5.4% (5.6%)
	3	2	2.6% (5%)	0	
	4	1	1.3% (2.5%)	0	
	5	1	1.3% (2.5%)	0	
Number of local treatments	**0**	49	62.8%	11	29.7%
	1	20	25.6%	17	45.9%
	2	5	6.4%	3	8.1%
	3	1	1.3%	3	8.1%
	4	2	2.6%	3	8.1%
	5	0		0	
	6	1	1.3%	0	
Number of systemic treatments	**0**	57	73.1%	36	97.3%
	1	19	24.4%	1	2.7%
	2	1	1.3%	0	
	3	1	1.3%	0	
Revisions (abutment change and soft tissue revision)	**0**	53	67.9%	28	78.4%
	1	19	24.4%	8	21.6%
	2	4	5.1%	0	
	3	2	2.6%	0	
Revision under general anesthesia	**0**	56	71.8%	32	86.5%
	1	16	20.5%	5	13.5%
	2	4	5.1%	0	
	3	1	1.3%	0	
Abutment removed	**0**	70	89.7%	37	100%
	1	8	10.3%	0	0%

Implant loss

Implant loss occurred in 4 patients (3.5% of all implants), in three patients within 2 months of implantation, in one patient after 2 years of follow up. Implant loss could not be linked directly to soft tissue problems in these patients; one patient however was treated with local treatment and systemic antibiotics multiple times in the months prior to the implant loss.

Table 4. Soft tissue outcomes - soft tissue reduction and abutment length during initial surgery (Birmingham) (excluding dermatome technique)

		Soft tissue revision		Abutment change	
	Total nr implants	**Nr implants**	**%**	**Nr implants**	**%**
Soft tissue reduction, 6mm abutment (follow-up mean 8.6 months, SD 4.7)	35	13	37.1%	16	45.7%
Soft tissue reduction, 9mm abutment (follow-up mean 6.8 months, SD 5.9)	10	2	20.0%	2	20.0%
Without soft tissue reduction, 6mm abutment (follow-up mean 9.2 months, SD 6.1)	8	1	12.5%	3	37.5%
Without soft tissue reduction 9mm abutment (follow-up mean 7.7 months, SD 4.5)	16	0		0	

Additionally, one patient presented with in intruded abutment after trauma (no implant loss) and needed surgery under general anesthesia for a new, longer abutment. In 5 patients the abutment was removed because of soft tissue problems in order to let the skin heal properly (3 patients with bilateral implants, both abutments were temporarily removed), from these, 1 patient was given a new abutment after 2.5 months. In the other 4 patients the abutments were not replaced before end of follow-up, a mean duration of approximately a year. Hearing rehabilitation was established with a bone conduction device on a softband or headband during the months of skin healing in these children.

Discussion

Principal findings

The aim of the current study was to verify a subjective increase of soft tissue problems in our pediatric BAHI population since the introduction of the BIA300. During mean follow-up of 11.7 months, 18 of 115 implants (15.7%) received local treatment for a soft tissue reaction on at least two occasions and in 32 implants (43.6% of implants with a Holgers notation, 27.8% of all implants) an adverse soft tissue reaction (Holgers 2 or higher) was noted at least once. In 28.7% of implants one or multiple revision surgeries were required, additionally, in five children the abutment had to be removed because of persistent soft tissue problems.

Comparison with other studies

Implant loss occurred in 3.5% of all implants in the current study. This is much less compared to what is described in literature for previous generation implants in children [7,9-12]. The reduced frequency of implant loss for the new generation implant was expected based on the results of implant stability studies in adult patients, seen in the clinical trial by Dun et al [2]. Implant stability studies on the BIA300 have also been conducted in pediatric population by McLarnon et al [13], Marsella et al [14] Felton et al [15] and Mierzwinski et al [16]. These studies report favorable results on implant stability for the new implant. Soft tissue outcomes were overall good, with only few adverse soft tissue reactions. The study by Mierzwinski et al focused additionally in more detail on soft tissue reactions using dermatome technique and single-staged surgery. In a total of 68 postoperative observations on the BIA300 with a follow-up of approximately 5 months post-surgery, this study recorded five adverse soft tissue reactions, i.e. Holgers grade ≥ 2 (7.4%). This percentage of soft tissue reactions is lower than what we found in our study. However, definitive conclusions for soft tissue outcomes are hampered due to the relatively small inclusion numbers and short follow-up.

If we compare the current results to reports from Birmingham and Nijmegen on soft tissue outcomes in previous generation implants, some differences are noticed. In a cohort on the previous generation implant and abutment by McDermott et al. [9], 24 out of 182 patients (13.2%) were considered to have adverse soft tissue reactions. Adverse was defined as a soft tissue problem requiring repeated visits to clinic for wound care, repeated silver nitrate cautery, or antibiotic therapy. Since we have chosen a different outcome measure in the current series, comparison of results is difficult. When we compare the number of patients who received multiple treatments in the current series with the outcome chosen by McDermott et al, no major differences are observed though. Regarding the outcome measure soft tissue revision, 7.7% of children required a skin revision in the series by McDermott at all, compared to 20.9% for both centers found in the current series (24.4% for Birmingham only in the current series). Longer abutment placement was needed in 8.2% in the previous series, compared to 25.2% in the current for both centers (28.2% for Birmingham only in the current series). This comparison is complicated by different follow-up duration, in the series by McDermott et al follow-up time was 4 to 13 years. This longer follow-up would, however, be expected to result in higher number of soft tissue reactions and revision surgeries.

De Wolf et al. [12] evaluated the results of the linear incision technique with previous generation abutments in the pediatric population. Adverse soft tissue reaction were recorded in 22.3% of all Holgers observations in this series, this is comparable to the number in the current series (18.9% adverse soft tissue reactions of all 290 Holgers observations). 14 of 129 patients (11%) needed revision surgery (soft tissue revision) in the study of de Wolf et al. Longer abutments were not discussed in this series as these were not yet available. In the current series, 28.7% of implants needed a soft tissue revision and/or longer abutment

because of soft tissue problems for both centers (21.6% for Nijmegen only in the current series). The same remark has to be made for this study regarding follow-up time; a much longer follow-up was available in the study by de Wolf et al. compared to the current study.

Soft tissue reactions are not easily to directly compare with previous studies, but they do not appear to have increased. Regarding revision surgery, an evident increase is observed. Whether this increase is a result of the new implant design or other causes, for example new surgical techniques, is not clear. Availability of longer abutments may be an explanatory factor for the increase in revisions (abutment changes). Nowadays many abutment changes are frequently carried out in the outpatient clinic, and the reduced need for general anesthesia may minimize reservations for revision surgeries. However, in many children an abutment change in the outpatient clinic will not be an option and excessive skin overgrowth can make this even more difficult in this setting.

The reported patient characteristics in the current study, do not differ much from what is described in the aforementioned studies. BMI, however, was not documented in our previous studies, so an increase in childhood obesity in general as explanatory factor cannot be excluded.

An extra remark has to be made on the sort of soft tissue reactions we noticed during the past few years. Previously, the surrounding soft tissue had complications for which local treatment was often adequate. Nowadays, more extensive overgrowth of the soft tissue over the abutment itself is noticed, while the skin often looks healthy and not particularly inflamed. In this case less response to medication was seen and revision surgery was needed to allow the sound processor to attach.

Strengths and limitations

The current study is the first report on soft tissue complications in a larger, multicenter series of the BIA300 in the pediatric patient population. The study included surgeries during the last three years, from which all records could be retrieved and the quality of information in the patient files was considered good. Retrospective review of charts is, however, well known to have problems with missing information. Another important limitation of the study was the mixed patient group. Between the two centers evident differences in patient and surgical characteristics were observed. Additionally, differences in postoperative protocol and treatment regimens were noticed. The evident difference in follow-up could be partly explained by the good attendance to the standard one-year visit in Nijmegen, where in Birmingham patients often only attend the standard one-year visit when having problems. The differences in patient characteristics might additionally be an important factor in the observed difference in soft tissue outcomes between the two centers, with results for the center including patients with less comorbidities being relatively more favorable. Moreover, the documentation of soft tissue reaction was in many cases unfortunately not according to the Holgers grading system. As a result we included other outcome measures as well,

such as the number of treatment regimens for local and systemic treatment. The absence of a uniform outcome reporting standard for all patients was a limitation in the current study, as well as the absence of a uniform standard in surgical strategy, i.e. linear incision versus U-shaped and dermatome and tissue reduction versus tissue preservation.

The differences noticed in the different surgical strategy groups, i.e. 6 or 9 mm abutment and soft tissue reduction at initial surgery, although large in numbers, should be interpreted carefully. Some differences were already noted in the recorded baseline characteristics of these patients and a confounding by indication in these results cannot be excluded.

Recommendations

For future research a prospective study would be warranted to give a more accurate insight in the discussed clinical outcomes, especially with respect to conclusions on results of initial placement of longer abutments and tissue preservation, as shown in Table 4. The authors would emphasize the importance of correct documentation of soft tissue reactions according to the Holgers grading system and full documentation of local and systemic treatments. This standardized evaluation is essential when new implants come to the market. As stated already in the introduction, since children are known to suffer significantly more from soft tissue problems, these clinical results should be closely monitored and reported. The increased number of soft tissue problems, especially revision surgeries, consequences of more visits to the outpatient clinic, and in some cases even lifelong treatments to soft tissue around the percutaneous abutment result in a higher burden rate for the patient, family and clinician, which should be taken into account. Specifically in the pediatric population, this might have a huge impact on time away from school and time way from work for many parents and caretakers. Moreover, when soft tissue problems become even worse, this can result in non-usage of the bone conduction device as seen in 5 children in this study. In these cases it may be necessary to remove the abutment and choose an audiological inferior solution such as the sound processor (or bone conduction device) on a softband or headband. Although in purpose a temporarily solution it turned out these patients were satisfied with this inferior solution in terms of audiological outcomes. It is important to realize that the kind of currently reported problems (skin overgrowth, removal of abutment, transfer to softband solutions) have not been reported before. Finally the soft tissue problems we noticed in the current study emphasize another important limitation of the BI300 implants, namely the incompatibility with other abutment systems. The choice of an abutment with a different shape or longer length other than the previously existing maximum 9 mm length in may offer alternative solutions to skin reduction surgery for these children with skin problems. Longer length abutments are currently only available with a hydroxyapetite coating which has not been fully evaluated in children

Conclusion

In summary, soft tissue reactions seem to be comparable to previous generation implants in the pediatric population. This in contrast to the adult population where less soft tissue reactions are noticed with the Cochlear™ BIA300 [6]. Revision surgery appears to be increased in the past few years. The continued peri-abutment skin problems and increased revision surgeries would result in more visits and a higher burden for the patient, family and the health-care system. However, as stated before, whether this is the result of the new implant or other factors cannot be concluded on the current series. Regarding stability, the BIA300 implant was shown to be a very stable implant system in this pediatric patient population, with an implant loss rate of 3.5%. Additional large and preferably prospective studies are needed in order to draw more firm conclusions in this specific and vulnerable population of children.

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chapter 4

The merits of bilateral application of bone conduction devices in children with bilateral conductive hearing loss

C.A. den Besten et al.

Work in progress

Objectives This study aims to demonstrate the differences in spatial hearing between bilaterally and unilaterally fitted bone conduction devices (BCDs) in children with bilateral conductive hearing loss (BCHL).

Design Both spatial discrimination and sound localization abilities were investigated. Spatial discrimination was measured with the minimum audible angle (MAA) test. Sound localization abilities were measured with a localization test. This test provides more detailed information about directional hearing, by presenting the stimuli at randomly selected locations in a dark environment and by roving stimulus levels. Ten children with congenital BCHL and one child with acquired BCHL participated.

Results Both spatial discrimination and sound localization scores improved with bilateral BCDs compared to the unilaterally aided conditions. However, discrepancies were found between both tests. While spatial discrimination showed good results in (nearly) all children, most children demonstrated sound lateralization rather than sound localization during the localization test. The child with acquired BCHL showed near-normal sound localization. Furthermore, it was noticed that children who were listening with one BCD did not use monaural (proximal sound level) cues for sound localization.

Conclusions Children with BCHL demonstrate a significant improvement in their sound localization abilities when listening with two BCDs compared to listening with a single BCD. Because both spatial discrimination and sound localization behaviour was tested, it could be demonstrated that sounds were lateralized rather than localized. The comparison between the two tests provides more insight in directional hearing capabilities of children with BCHL who are listening with BCDs.

Introduction

Bone conduction devices (BCDs) are one of the treatment options for rehabilitating conductive hearing loss [1,2]. For patients with bilateral conductive hearing loss (BCHL), application of bilateral BCDs has shown to be beneficial compared to application of a unilateral BCD [3-6]. Several reviews suggested that more studies are needed to provide evidence on the advantage of bilateral BCD application over a unilateral BCD [7,8]. Moreover, bilateral application is not standard of care in all clinics and in some countries not (fully) reimbursed [9].

The advantage of bilateral over unilateral application of BCDs is related to bilateral input and potentially to binaural hearing (i.e. processing of binaural cues) [10,11]. The latter depends on accurate processing of interaural differences in level (ILDs) and timing (ITDs). Testing and demonstrating the accuracy of processing binaural cues can be done using an operational tool like a sound localization test [12]. Unfortunately, the set-up of sound localization tests is not standardized. They range from setups with a few loudspeakers positioned in the azimuth plane 60^0 apart [13], to setups were stimuli can be presented from many different positions [14,15]. Furthermore, the setups differ in: i) response method, ii) stimulus bandwidth, iii) stimulus duration, iv) loudspeaker visibility, v) sound level roving.

Several studies have reported good results on subjective benefit of bilateral BCDs and on effective daily use of both devices, both in adult and paediatric patients [16-18]. Audiometric evaluation of bilaterally fitted BCDs demonstrated improved speech recognition in noise with spatially separated speech and noise sources, and improvements in sound localization [3,5,6,19-22]. Only three of these studies were performed in children [4,6,20]. The advantage of bilateral BCDs was less pronounced in children with congenital BCHL compared to adults [4]. In general, in case of hearing with bilaterally applied BCDs, limited transcranial attenuation of bone conduction vibrations results in concomitant stimulation of the contralateral cochlea (cross-stimulation) [23]. This could affect accurate perception of ILDs and ITDs, and consequently hamper proper binaural hearing. However, literature has implied that patients with congenital BCHL can detect ILDs and ITDs [24]

The aim of the present study was to strengthen the evidence on the added value of bilateral BCDs over unilateral BCDs in children with BCHL by evaluating spatial hearing. By including both a spatial discrimination and a sound localization test we aim to demonstrate whether bilaterally fitted children can indeed utilize binaural cues.

Material And Methods

Patients with bilateral conductive hearing loss (BCHL)

We identified 33 children (implanted at 6-16 years) with BCHL and bilateral percutaneous bone conduction hearing implants from our clinical database. All children had at least

6 months experience with two BCDs. For the directional hearing tests children with a performal IQ ≤ 80 and/or poor co-operation during previous testing (n=6) and temporarily using just one BCD (n=5) were excluded. We could not find up-to-date contact details for three children. Finally, we invited 19 children to participate in the hearing tests, and parents or caretakers of 11 children agreed to participate. Four of these 11 children took part in a previous study on directional hearing [6].

Table 1. Demographic and audiological characteristics of the participating children. PTA4 = pure tone averaged of 0,5-1-2-4kHz, AD = right, AS = left, AC = air-conduction, BC = bone-conduction, C = congenital, A = acquired, X = no data, Time is indicated by months (M) and/or years (Y).

	Sex	Age at current evaluation	Age at BCD implantation***	Age at first hearing aid fitting	Age at two hearing aids fitting	Type of hearing loss	Etiology	Syndrome	Current sound processors	PTA4 AD AC	PTA4 AD BC	PTA4 AS AC	PTA4 AS BC
P1	F	7Y	4Y	3M**	1Y	C	Atresia III	Goldenhar	Baha 4	59	1	74	5
P2	F	7Y	4Y	4M**	1Y 11M	C	Ossicular chain anomalies	Goldenhar	Baha 4	59	-1	58	8
P3	M	7Y	4Y	5M**	1Y 5M	C	AS Atresia III AD Atresia I	Goldenhar	Divino	32	-3	61	10
P4	F	7Y	5Y	1Y**	4Y	C	Atresia IIa	De Grouchy	BP100	60	4	60	3
P5	F	8Y	4Y	7M**	5Y	C	Atresia III	Treacher Collins	Divino	75	15	70	13
P6	F	8Y	7Y	1y 3M**	4Y	C	Atresia ill	Treacher Collins	BP100	64	0	59	-
P7	M	9Y	4Y	1y 9M**	4Y	C	Atresia III (reconstruction microtia ADS + external auditory canal AD)		BP100	34	-1	70	6
P8	F	14Y	6Y	9M**	2y 12M	C	Atresia III		BP100	61	4	64	8
P9	M	15Y	7Y	2M**	7Y****	C	Atresia III		BP100	53	3	68	10
P10	M	16Y	6Y	1y 7M	6Y****	C	Atresia IIa		Divino	54	3	58	0
P11*	F	16Y	11Y	8Y	8Y	A	Chronic otitis media		Divino	44	10	66	10

* child P11 had acquired bilateral conductive hearing loss and used air-conduction hearing aids up till age 8

** used one BCD on (soft)band before implantation (alternately right/left ear or medially)

*** 2-phased bilateral simultaneous percutaneous bone implant surgery

****rehabilitation elsewhere, referral at this age to our center for percutaneous bone implant surgery

Of the 11 children, one had an acquired BCHL while ten children had congenital BCHL due to microtia/aural atresia. Table 1 presents the characteristics of the 11 participants. Congenital BCHL due to bilateral microtia/atresia is a relatively rare condition with an incidence of 1:50.000 newborns [25]. Hence, it is important to provide these patients and their caretakers with evidence on outcomes on hearing rehabilitation, like spatial hearing.

Age and sex distribution of the 11 participants were comparable to those of the whole group of 33 BCHL children. The whole group contained relatively more acquired cases (6 out of 33) than the test group (1 out of 11). All children in the test group used their BCDs intensively; six days a week (N=1), and seven days a week (N=10). Children used their BCDs either 8 to 12 hours a day (N=2) or more than 12 hours a day (N=9). All children were either satisfied (N=4) or very satisfied (N=6) with their devices. The answer of one child is missing. A slightly lower usage time was noted in the whole group (N=2 out of 29 usage 6 days a week and N=3 usage less than 6 days a week; N=3 usage less than 8 hours a day and N=9 usage 8 to 12 hours a day). Additionally, as expected with an exclusion criterion of IQ<80, the education level was higher in the test group compared to the whole group of 33 children.

The hearing tests were performed with the child's own devices (either Baha Divino, Baha BP100, or Baha 4; Cochlear BAS, Gothenburg). All BCDs were set in auto- or omnidirectional microphone mode and tests were performed with the child's own habitual volume settings. The BCD conditions were randomized: unilateral BCD on the left side, unilateral BCD on the right side and bilateral BCDs.

This study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee.

Minimum Audible Angle (MAA) Test

Ten out of eleven children were tested with the MAA test. This test measures the smallest difference in the position of two sound sources in the horizontal plane, in the frontal position [2,26,27]. A broadband noise (BB noise; bandwidth 0.5-20 kHz, 500 ms duration) was presented at three randomly selected sound levels of 55, 60, 65 dB SPL. The sound level was roved to minimize effects of head shadow as a monaural localization cue [28]. The MAA test was carried out in a sound attenuated booth; the children were positioned in the centre of an arc with a 1-m radius. After a practice run, the loudspeakers were positioned at -90^0 (far left) and $+90^0$ (far right). Stimuli were presented at random by one of the two loudspeakers and the child was asked to identify the loudspeaker. After four correct responses out of four stimuli, the loudspeakers were repositioned to -60^0 and $+60^0$. This procedure was continued for positions at 30^0, 15^0, 10^0 and 5^0. In case of an incorrect answer, a series of four stimuli was presented in the previous speaker position. The final score was defined as the smallest angle at which a series of four stimuli was correctly identified in two out of three runs. No feedback was given during the measurements.

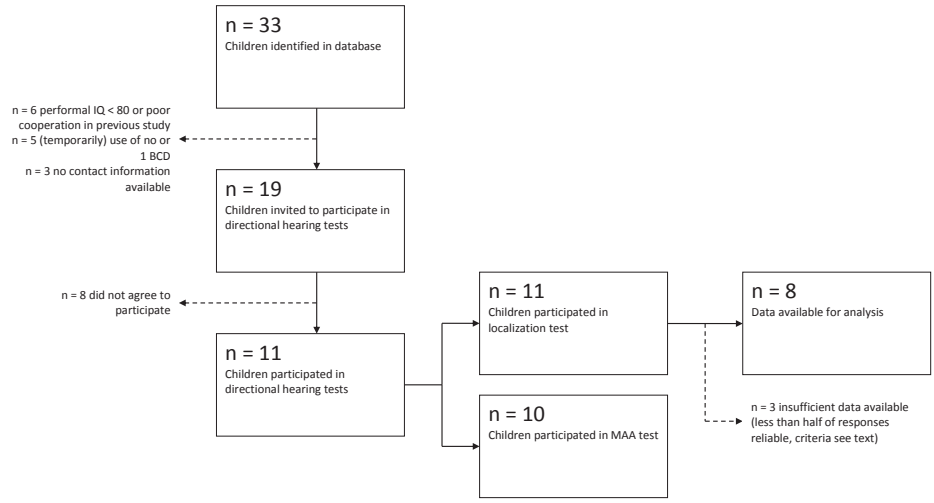

Figure 1. Flowchart of the children with BCHL eventually participating in the experiments.

Sound localization test

Sound localization was tested in all eleven children, but the data of only eight children could be used for analysis. The localization experiment was conducted in a dark and sound-attenuated room. Children were seated in the centre of the room. Stimuli were delivered from loudspeakers at a distance of 1.15 m from the child. Stimuli were presented at different azimuth positions, ranging from -75^0 (left) to $+75^0$ (right). The broadband (BB; bandwidth 0.5-8kHz) noise bursts with a duration of 150 ms, were at random presented from selected speaker locations, at three random sound levels of 50, 60 or 70 dB SPL. A complete trial comprised 36 stimuli. The response task was a head movement towards the noise source. Head movements were recorded with the magnetic search-coil induction technique [29], which has been shown to be adequate for testing normal hearing children [30] and hearing impaired children [31].

Each child participated in a short practice session at the beginning of the experiment. During the measurements, children were only corrected when distracted or when they were in an incorrect seating position; no other feedback was given. The unilateral and bilateral aided conditions were tested in a random order. The perception of ILD and/or ITD was studied separately by testing the four oldest children with an additional set of stimuli in the bilateral BCD condition only. This set included 60 stimuli, BB (12 stimuli at 60 dB SPL), low-frequency (bandwidth 0.5 to 1.5 kHz; 12 stimuli at 60 dB SPL), and high-frequency noise bursts (bandwidth 3 to 20 kHz; 36 stimuli at roved sound levels: 50, 60 and 70 dB SPL). The 60 stimuli were presented interleaved.

Localization of visual stimuli

Some of the younger children (7-8 years old) had difficulties with performing and/or completing the sound localization task. To investigate whether this was related to their impaired hearing or related to understanding and execution of the task, a visual localization task was additionally performed in three of the younger children (P1, P3 and P5) by replacing the auditory stimuli by visual stimuli at the position of the loudspeakers. A series of 36 visual stimuli (duration 150 ms) was presented with light-emitting diodes.

Data analysis

Spatial discrimination (MAA) and sound localization data were analysed for each child and each condition separately. Data of the localization test for three individual subjects (P6, P10 and P11) are shown as stimulus-response plots in Figure 2. Because the data of the bilaterally aided condition was not uniformly distributed, linear regression analysis (as done usually) was not feasible. Consequently, linear regression was only carried out for the unilaterally aided conditions In these conditions, the bias is expected to be towards the site of the BCD, consequently negative when the left BCD is active, and positive when the right BCD is active. The MAE is the mean of all the (absolute) errors, in degrees, between the azimuth response and the position of the target loudspeaker. This measure does not rely on regression analysis and can thus be used for both the unilateral and bilateral conditions.

We adopted the following criteria for analysing the localization data i) each trial begins with a stable head position between -20^0 and $+20^0$, ii) head movement starts at least 150 ms after stimulus onset and iii) head movement ends with a stable head position for at least 250 ms. The dataset of a condition was included for further analyses when at least half of the responses were reliable. These criteria resulted in including only 8 out of 11 datasets for analysis.

Further analysis of the localization data in the unilateral aided condition (left and right side only) was conducted to evaluate the possible contribution of the head shadow effect (i.e. usage of sound levels as a localization cue, despite of roving) in comparison to the actual target azimuth [28,32]. A standardized multiple linear regression analysis was performed to separate the contribution of the azimuth stimulus coordinates and of the stimulus intensity at the BCD position (i.e. head shadow effect) on the azimuth response. Normal hearing listeners rely on the actual azimuth coordinates as a cue and consequently present with an azimuth coefficient around one and a proximal sound level coefficient (i.e. the coefficient for the stimulus intensity at selected BCD) close to zero. A proximal sound level coefficient close to one with an azimuth coefficient around zero illustrates the listener's localization abilities rely on perceived sound level (using head shadow cues). These data were compared to those of adult normal hearing listeners and patients with single sided deafness from a previous study [32].

Data analysis was done using Matlab (the MathWorks) and Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Armonk NY; IBM Corp, Version 22).

Results

Bilateral BCDs improve spatial discrimination of sounds and directional hearing

In Table 2 the outcomes of the spatial hearing tests are presented. Some of the younger children could not be tested in all conditions. Both the MAA outcomes and the sound localization outcomes show a clear improvement when listening with two BCDs as compared to listening with one BCD (paired samples *t*-test MAA $p<0.001$). In 8 out of the 10 tested children, the MAA improved from 60^0-90^0 in one of the unilateral conditions to $\leq 15^0$ in the bilateral BCD condition. Only one child (P5) did not demonstrate an improvement when listening with two BCDs; the MAA was 90^0 in all conditions. Surprisingly, in the unilateral conditions of the MAA, this subject did not perceive all stimuli at the aided side, in contrast to the other children. The localization data of this child were not included in the analysis, due to a small number of reliable data points. Also, this child was only tested in the bilateral condition.

Table 2. The minimum audible angle (MAA), bias and mean absolute error (MAE) results of all children (P1 – P11) for the unilateral aided left, unilateral aided right and bilateral conditions with BB stimuli. All measures are expressed in degrees.

	Unilateral Left			**Unilateral Right**			**Bilateral**		
	MAA	**Bias**	**MAE**	**MAA**	**Bias**	**MAE**	**MAA**	**Bias**	**MAE**
P1	90	6	68	90	37	61	15	N.A.	38
P2	15	-	-	60	-	-	5	N.A.	-
P3	90	-59	66	90	63	67	15	N.A.	51
P4	90	-	-	90	-	-	10	N.A.	-
P5	90	-	-	90	-	-	90	N.A.	-
P6	90	-52	54	90	49	55	5	N.A.	19
P7	-	-28	58	-	-	-	-	N.A.	53
P8	90	-65	72	30	81	83	5	N.A.	28
P9	90	-32	51	90	39	55	30	N.A.	36
P10	15	-31	46	90	61	69	5	N.A.	45
P11*	60	-42	52	90	48	52	10	N.A.	10

* acquired conductive bilateral hearing loss

Figure 2 shows exemplary stimulus-response plots for three listeners with distinctive response patterns (P6, P10 and P11), for BB stimuli. Responses of the three sound levels were pooled. The bias and MAE are indicated when appropriate. Stimulus-response plots for both the unilateral BCD and the bilateral BCDs conditions are presented. The localization abilities in the unilateral BCD conditions are clearly impaired. In the unilateral condition, stimuli are mainly perceived at one location. For example in child P6, the bias in the unilateral left condition is -52^0 and in the unilateral right condition 49^0. An exception is the unilateral BCD-left condition of P10, which shows a different response pattern. This was the only child that reported a preference for the left BCD when using only one BCD.

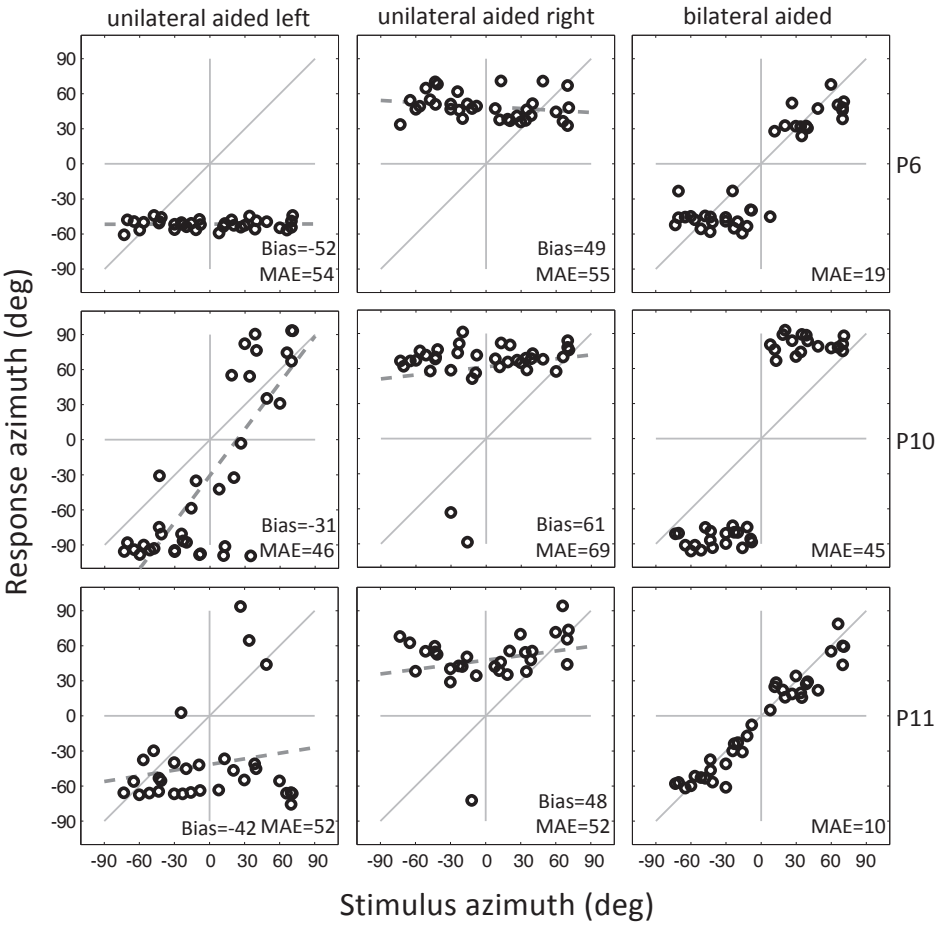

Figure 2. Sound-localization stimulus-response plots for children P6, P10 and P11. Responses of the three sound levels (50, 60 and 70 dB SPL) are pooled and plotted for BB noise bursts in the unilateral left (left column), unilateral right (middle column) and bilateral (right column) BCD condition. P6 and P10 demonstrate lateralization of stimuli in the bilateral BCD condition while P11, the only patient with acquired bilateral conductive hearing loss, demonstrates good localization abilities. MAE = Mean absolute error, in degrees.

In the bilateral aided condition, P6 and P10 demonstrated bimodal response patterns reflecting sound lateralization and not localization behaviour. These two children were able to discriminate left and right stimuli, but they could not identify the correct sound location. Patient P11 with an acquired BCHL does seem to be able to localize in the bilateral aided conditions, since the majority of data points lie along the diagonal and yielded a small thus profitable MAE of 10°. Localization performance of P11 (gain = 0.91, r^2 = 0.93, bias -4.5) is close to that of normal hearing children (gain = 0.91, r^2 = 0.97, bias 7.7°) [30]. The results of this child indicate that it is possible to process binaural cues properly when listening with two BCDs.

In Figure 3 the MAE of the bilateral aided condition is plotted against the MAE in both unilateral conditions. Each data point represents one child. The aided left condition is marked by black circles and aided right by white circles. The three children (P6, P10, P11) of Figure 2 are indicated. The asterisk represents the child with an acquired BCHL (P11). The bold black line represents the mean of normal-hearing controls and the grey area illustrates ±2 standard deviations [32]. In this figure all data points are above the diagonal, meaning that the MAE is smaller (better) in the bilateral condition than in the unilateral conditions. However, only child P11 is within the normal range (grey area). In the unilateral conditions (vertical axis), generally, spatial discrimination was poor (MAE > 50^0) with an obvious bias towards the side with BCD (see Table 2; bias generally > 0 degrees for the unilateral right condition and < 0 degrees for the unilateral left condition). Patient P7 and P10 showed minimal improvement in the bilateral aided condition compared to aided left condition (Figure 3, data point close to the diagonal). A significant difference between the MAE unilateral aided left (58.3°) and right (63.1°) to the bilateral aided (35°) condition was found (paired *t*-test, $p = 0.002$; $p = 0.001$).

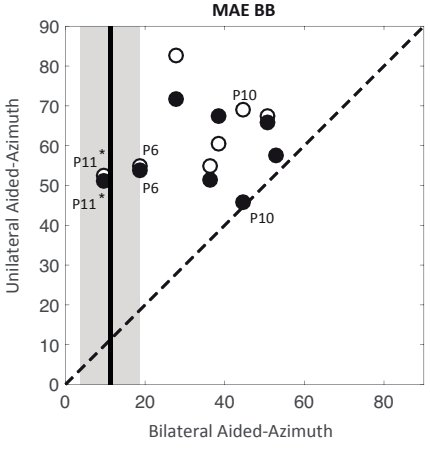

Figure 3. Sound localization test: Mean absolute error (MAE) in degrees. The unilateral aided left (black circles) and unilateral aided right (white circles) condition are plotted against the bilateral condition, for broad band (BB) stimuli. Data points from the children depicted in Figure 2 (P6, P10 and P11), are indicated in the figures. Also, average localization scores (vertical black lines) ± 2 standard deviations (grey area) of normal hearing listeners are shown. Asterisk (*) indicates the only patient (P11) with acquired BCHL.
**P7 was not tested in the aided right condition, hence, one less data point than in the aided left condition is plotted.

The four oldest children (age ≥ 14y, P8-P11) were additionally tested on their sound localization abilities using broad-band, low-pass and high-pass noise bursts interleaved, to study the effective use of ILDs and ITDs separately. No major effect is observed for these participants in their stimulus-response patterns when stimulated with low-frequency, high-frequency and broadband noise bursts. Formal statistical testing was not performed due to small sample size.

Proximal sound level cues

Further analysis was carried out to quantify the contribution of the head shadow effect when localizing with one BCD. The results are shown in Figure 4. Each data point represents one listening condition (aided left condition = black circles; aided right condition = white circles). The grey square indicates scores for normal-hearing listeners with an azimuth coefficient around one and proximal sound level coefficient close to zero, indicating optimal use of azimuth information and not relying on level cues. The black line schematically represents previously reported results from patients with long-term unilateral hearing (second ear deaf, single-sided deafness or SSD) [32]. These patients effectively used sound level cues for localization. In Figure 4 the data of the children in the unilaterally aided condition scatter mainly around a proximal sound level coefficient and an azimuth coefficient of 0 to 0.5. These low coefficients indicate that, in contrast to the SSD patients, the studied children with BCHL listening with one BCD do not use monaural cues.

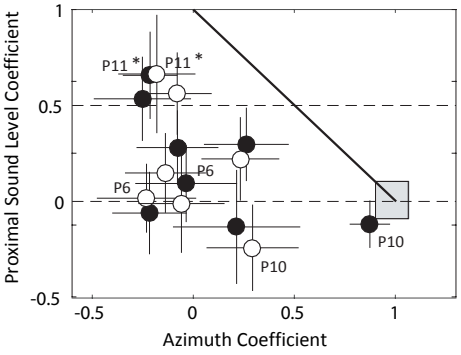

Figure 4. Proximal sound level coefficient (y-axis) plotted against azimuth coefficient (x-axis) of unilateral aided left (black circles) and unilateral aided right (white circle) conditions for broadband (BB) stimuli in all tested patients. Grey coloured square is a schematic representation of the results from unaided SSD patients; [32]. Children from figure 2 (P6, P10 and P11) are indicated. Asterisk (*) indicates the only acquired hearing loss patient (P11).
** A partial correlation analysis was performed to dissociate the potential contribution of the proximal sound level from the actual stimulus location.

Visual condition versus hearing condition

Figure 5 demonstrates accurate localization of visual stimuli in two of the youngest children (P1 and P3) and therefore demonstrates that the inaccurate localization of auditory stimuli is related to impaired hearing abilities, and not to limitations of understanding and performing the test.

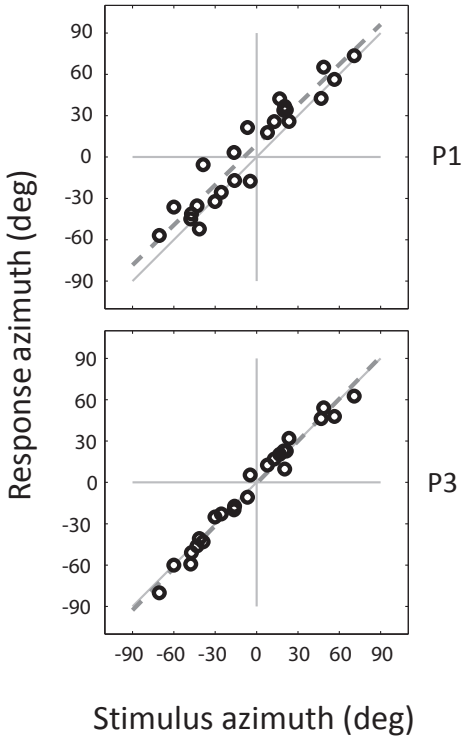

Figure 5. Azimuth stimulus-response plots for visual stimuli only of the two youngest children. The dashed lines denote the linear regression line.

Discussion

This study demonstrates the importance of bilateral application of BCDs in children with BCHL. When fitted with one BCD, all children had great difficulty in discriminating horizontal sound positions. In this condition the majority of children had a minimum audible angle > 60^0. In the sound localization test, children perceived the stimuli mainly at one position, on the aided side. When fitted with both BCDs, spatial discrimination, as well as directional hearing, improved. However, directional hearing in the bilaterally aided condition can be characterized as 'lateralization' instead of 'localization'. Bilaterally fitted children can distinguish sounds coming from left or right side, but they cannot indicate the exact sound source location. The results from the localization test were validated with a visual localization test in the two youngest children (P1 and P3). This visual control test demonstrated that visual stimuli were correctly localized, indicating that the children did not experience problems with the test procedure, so poor scores on the sound localization test indeed relate to poor sound localization abilities.

The variation in proximal sound level coefficients in the unilateral aided condition (Fig. 4) indicates a different behaviour compared to subjects with single-sided deafness [32]. In contrast to SSD, children with microtia and/or aural atresia do not have access to spectral

(pinna) cues due to their ear anomaly. Also, head shadow induced sound level cues were hardly used. Hence, our data strongly support the importance of a second BCD for patients with BCHL to enable optimal directional hearing. Although the main benefit is improved lateralization rather than exact localization, the second BCD is beneficial, as sound localization with one device is absent. Especially promising is the good sound localization ability with two BCDs of patient P11 (best performer), with almost normal results. This child was the only child with acquired BCHL, suggesting that binaural experience might be beneficial. The worse localization results in the congenital cases might indicate that a sensitive period for the development of binaural hearing exists. Bosman et al. (2001) however, found good localization in a group of adults with bilateral conductive or mixed hearing loss using two BCDs, with limited differences between acquired and congenital onset. These results indicate that the brain is plastic and not in line with our results. Further research on these differences seems indicated.

Another interesting finding is the good localization ability of P10 in the unilateral BCD-left condition. This was the only child reporting a preference for using the left BCD over the right BCD for the unilateral condition. This child was initially, before implantation, fitted with a BCD on a softband on the left side, whereas all other children alternated BCD usage between left and right side.

Earlier studies have also shown benefits of bilateral BCDs and effective daily use of both devices [16,17,18]. Since the current evaluation only provides data on usage time and some subjective data, searching for a link between subjective and objective results would not be accurate. All previous studies have either focused on audiometric and spatial hearing tests, or on subjective benefit. It would be interesting to explore this combination in more detail.

The current study was limited to children with BCHL and bilateral BCDs and did not include children with one implant. In our study the unilaterally aided condition was rather new to all children, i.e. the children were accustomed to listening with bilateral inputs and not to an 'acute' unilateral input. This acute condition might have influenced our results, i.e. long-term unilateral rehabilitation of patients with BCHL might present different unilateral results. Especially, long-term experiences with one BCD might result in more effective use of monaural cues like the proximal sound level cue.

With respect to a choice between both tests, the MAA test is well suited to show an advantage of bilateral versus unilateral application of BCDs. Since the MAA test is easy to conduct, it might be the preferred clinical test, especially in young children. However, to study directional hearing (e.g. assessing binaural processing and the use of (monaural) intensity and frequency cues) a full sound localization test is preferred.

To conclude, our results emphasize the need for bilateral BCD application in children with BCHL. Despite obvious inter-subject variability, the advantage of bilateral BCDs over unilateral BCDs was outspoken, especially with respect to lateralization. Directional hearing is important in daily life, for example in the classroom but also for understanding

speech in noise (especially in children developing speech and language abilities). Optimal localization abilities are expected to improve safety outdoors, as this might decrease traffic risks [33]. In many practical situations sound sources are also visible. In these cases sound lateralization as seen in the children with a bilaterally fitted BCD, might be sufficient for audio-visual source localization. However, this situation is obviously less optimal compared to a situation with adequate localization, hence counselling of parents and children on these differences is deemed necessary. Additionally, behavioural training programs (using this audio-visual input) might improve directional hearing and should be considered as a topic for future research as this might include a potential therapeutic strategy [34,35].

The current study focuses on results of bilateral input of percutaneous BCD's on directional hearing in patients with (mainly congenital) bilateral conductive hearing loss. Other advantages of bilateral rehabilitation (usage of head-shadow in noise and binaural summation amongst others) are not included. Nonetheless, these important benefits are available in bilaterally rehabilitated children. In conclusion, given the known advantages of bilateral rehabilitation and the current results on directional hearing, bilateral application of BCDs in children with BCHL is advocated.

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Part II

New implants and surgical technique

chapter 5

Stability, survival, and tolerability of an auditory osseointegrated implant for bone conduction hearing: long-term follow-up of a randomized controlled trial

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Objective To compare implant stability, survival and soft tissue reactions for a novel (test) and previous generation (control) percutaneous auditory osseointegrated implant for bone conduction hearing at long-term follow-up of 5 years.

Study design Single follow-up visit of a previously completed multicenter, randomized, controlled trial.

Patients Fifty-seven of the 77 participants of a completed randomized controlled trial on a new auditory osseointegrated implant underwent a single follow-up visit five years after implantation, which comprised implant stability measurements and collection of Holgers scores. Additionally, implant survival was recorded for all 77 patients from the original trial.

Results The test implant showed significantly higher implant stability quotient (ISQ) values compared to the control implant throughout the 5-year follow-up. Mean area under the curve of ISQ high from baseline to 5 years was 71.6 (SD ±2.0) and 66.7 (SD ±3.4) for the test and control implant, respectively ($p<0.0001$). For both implants, the mean ISQ value recorded at 5 years was higher compared to implantation (test group +2.03 (SD ±2.55, within group $p<0.0001$) and control group +2.25 (SD ±4.95, within group $p=0.12$)). No difference was noticed in increase from baseline between groups ($p=0.64$). Furthermore, evaluation of soft tissue reactions continued to show superiority of the test implant. At the 5-year follow-up visit, one patient (2.5%) presented with a Holgers grade 2 in the test group, compared to four patients (23.5%) in the control group ($p=0.048$); no patient presented with more severe soft tissue reactions. Excluding explantations, the survival rate was 95.8% for the test group and 95.0% for the control group. The corresponding rates including explantations were 93.9 % and 90.0 %.

Conclusion The test implant showed superiority in terms of higher mean ISQ values and less adverse soft tissue reactions, both at the single 5-year follow-up visit and during the complete follow-up. In addition, both implants showed an equally high implant survival.

Introduction

Since Tjellström reported on the fitting of the first patient with a bone-anchored hearing device using a temporal bone implant in 1977 [1], many improvements have been made to auditory osseointegrated implant systems (also referred to as bone conduction hearing implant systems). Hearing rehabilitation through direct bone conduction via an implant anchored in the temporal bone is nowadays an established method to overcome pure conductive hearing loss and also for mixed hearing loss as well as single-sided sensorineural deafness [2]. The original auditory osseointegrated implant was a titanium implant with an as-machined surface, designed by Brånemark in the late 70's and later made commercially available as the Cochlearä Bahaâ flange fixture. In 2009, a new implant design was introduced, with a wider diameter aimed to increase implant stability [3] and a moderately roughened surface to increase bone response (i.e. remodeling) after implantation [4]. Moreover, a new rounded shape and conical connection that provides a tighter seal to the percutaneous abutment were chosen to reduce soft tissue reactions. Previously, Dun et al. and Nelissen et al. reported 6 month and 3-year results from a randomized controlled trial of this new (test) implant and previous generation (control) implant [5,6]. Implant stability measurements showed higher mean implant stability quotient (ISQ) values during the complete follow-up period for the test implant compared to the control implant. An initial decrease in stability was recorded 10 days after surgery in both study groups, while ISQ values remained relatively stable above baseline scores across the 6, 12 and 24 months visits. However, a statistically significant decrease towards baseline was noticed for both implants at the last follow-up visit at three years. Better soft tissue outcomes were observed with the test implant, while implant survival after three years was comparably high for both implants.

While formally a separate study, the current clinical investigation is a continuation of the previously completed and reported trial with a single follow-up visit five years after implantation [5,6]. The aim of the current study was to measure long-term implant stability and explore the development of the decreasing ISQ values seen at the 3-year follow-up visit, and to confirm good implant survival and abutment tolerability at long-term follow-up. The current results comprise the first 5-year clinical data collected prospectively on percutaneous auditory osseointegrated implants.

Methods

Study design and participants

The aim of the current study was to show superiority of the test implant compared to a control implant in terms of implant stability (primary outcome measure), and to evaluate long-term implant survival and soft tissue reactions (secondary outcome measures).

The study was designed as a single prospective follow-up visit five years after implantation for the patients who participated in the completed 3-year multicenter, randomized, controlled trial conducted at Radboud University Medical Centre Nijmegen (Nijmegen, The Netherlands), Salford Royal Hospital (Salford, UK), Sahlgrenska University Hospital (Göteborg, Sweden) and Manchester Royal Infirmary (Manchester, UK). All patients who participated in the original trial were invited to participate in the current study. To be included in the original trial, the patients had to be at least 18 years old, have a bone thickness at the implant site of at least 4mm, and no disease or treatment known to compromise the bone quality at the implant site. Exclusion criteria for the current study were inability to follow investigational procedure and any factor, at the discretion of the investigator, that was considered to contraindicate participation, e.g. mental or physical disability or travelling plans not compliant with the study protocol. For patients who had lost or removed the implant placed in the original trial, only time to implant loss was recorded. Patients who for other reasons did not attend the 5-year visit were also included in the implant survival analysis; the last available information regarding implant survival was obtained verbally from the patient, from medical records or from information captured in the original investigation.

Randomization for the original investigation was fixed in proportions 2:1 (test:control), stratified for each site, and was realized by means of numbered blinded envelopes. Both patients and surgeons were blinded until implantation, but because of differences in implant design, no blinding could be applied thereafter. Surgery was performed between April and December 2009. A single-stage surgical procedure with reduction of subcutaneous soft tissue was applied in all centers; a linear incision technique was used in Nijmegen, the flap technique in Manchester and Salford, and the dermatome technique in Göteborg. At each site, the same technique was used for test and control implants. Loading of the implants with sound processors was performed from 6 weeks after implantation. Follow-up visits in the previous study were completed at 10 days, at 4, 6, 8, and 12 weeks, and at 6, 12, 24 and 36 months.

Implants

The test implant was the novel titanium implant (diameter 4.5 mm; length 4mm) with a 6 mm rounded, apically converging titanium abutment developed by Cochlear Bone Anchored Solutions AB (Mölnlycke, Sweden). This system was later commercialized under the name Cochlearä Bahaâ BIA300 Implant with Abutment with an additional minor change to the internal abutment connection design. The control implant was the previous generation as-machined titanium flange fixture (diameter 3.75 mm; length 4mm) with a 6 mm conically shaped abutment from the same manufacturer. Aside from the difference in abutment shape, the test implant incorporates a wider diameter, small-sized threads at the implant neck, and the moderately rough TiOblastä (Dentsply, Mölndal, Sweden) surface on the intraosseous part of the implant (Figure 1).

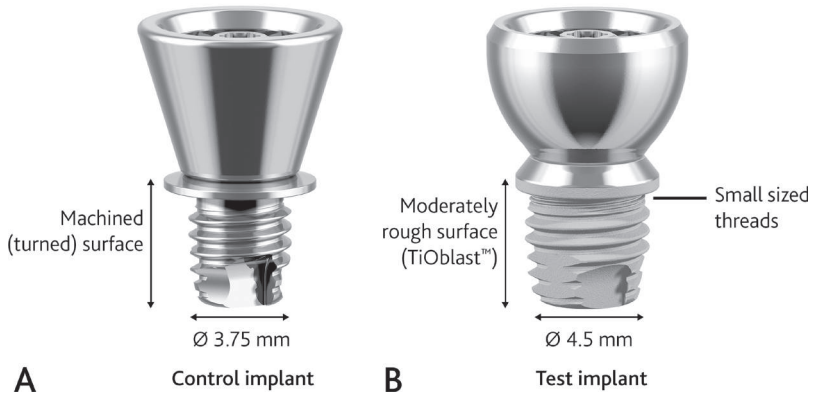

Figure 1. Control (A) and test (B) implants with abutments

Outcomes of the 5-year follow-up visit

For all patients who attended the single visit, demographics, baseline variables (date of birth, gender, ethnical background, use of nicotine) and relevant medical history since the previous study were recorded. Implant stability quotient (ISQ) values were measured using resonance frequency analysis (RFA) at the abutment level with the Osstell Mentor or Osstell ISQ and a SmartPeg (type 43) (Osstell AB, Göteborg, Sweden). The ISQ score ranges from 1 to 100, with increasing scores presenting a more rigid implant-bone interface. As this score is also a representation of other implant variables, assessment of changes over time is consequently more sensible than evaluation of absolute values at a given time point [7,8]. The highest (ISQ high) and lowest value (ISQ low) obtained from perpendicular measurements were recorded. Soft tissue status was assessed according to the Holgers soft tissue classification on a 5-point scale from 0, no signs of soft tissue reaction, to 4, an infection requiring implant removal [9]. Holgers grade 2 or higher is considered an adverse soft tissue reaction in need of (local) treatment and the distinction is consequently of clinical importance. Furthermore, implant survival/loss was recorded, including the reason of implant loss or explantation (active removal of the implant).

Statistical analysis and data management

No new sample size calculations were performed; all patients from the previous investigation were asked to participate. For the original study a power calculation was conducted on the primary outcome variable ISQ [6]. For comparisons between test and control groups, Mann-Whitney U test was used for all continuous variables, Mantel-Haenszel chi-square test for all ordered categorical variables, and Fisher exact test for dichotomous variables. Wilcoxon Signed Rank test was used for change within groups for continuous variables. A weighted average of ISQ during the entire study period was obtained by mean area under the curve (AUC) calculations. Implant survival probability was analyzed using a

Kaplan-Meier survival curve with log-rank test; the last available information regarding implant survival was used as the censoring date for the implant survival analysis.

A significance level of 0.05 was adopted and all tests were two-tailed. No corrections were made for multiple comparisons. For the primary outcome variable, in case of missing baseline value the value at the second visit was used as baseline value instead; furthermore, no imputation with last observation carried forward was used.

Data management was performed by external data managers (dSharp, Göteborg, Sweden, and Statistiska Konsultgruppen, Göteborg, Sweden), and statistical analysis was realized by external biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden) according to a predefined statistical analysis plan using SASâ v9.4 (Cary, NC, USA).

Ethical consideration

The investigation was conducted in accordance with the Declaration of Helsinki and the international standard for 'Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2011). Local ethics committees and competent authorities in all participating countries gave approval or a declaration of no objection for this single follow-up visit after 5 years.

The current study was registered at ClinicalTrials.gov and assigned the identifier NCT02092610.

Results

Patient characteristics

Out of the 77 patients in the original study, 57 patients (37 in Nijmegen, 11 in Salford and 9 in Göteborg) signed the informed consent to participate in this follow-up trial and attended the five-year follow-up visit. While the study protocol indicated a visit window of 60 ± 3 months, the actual visit dates ranged from 60 to 71 months post implantation. The patients from Manchester Royal Infirmary (Manchester, UK) could not visit the clinic, but were included in the implant survival population.

Twenty patients were lost to follow-up, had lost their implant or were not able to visit the clinic. The baseline characteristics of the 57 patients who attended the study visit ('five-year follow-up population') and the 77 patients in the original trial (who constituted the 'implant survival population' in the current investigation) are shown in Table 1. A slightly older patient population was seen for the control implant, which was more evident in the five-year follow-up population. There were no other significant or important differences in baseline characteristics between the two study groups.

Table 1. Baseline characteristics

Characteristics		Five-year follow-up population (n=57)*		Implant survival population (n=77)*	
		Test group (n=40)	Control group (n=17)	Test group (n=52)	Control group (n=25)
Sex	**Male**	19 (47.5 %)	10 (58.8 %)	23 (44.2 %)	15 (60.0 %)
	Female	21 (52.5 %)	7 (41.2 %)	29 (55.8 %)	10 (40.0 %)
Age at baseline**	**Years**	55.4 (SD 12.8; range 22.1-78.8)	64.2 (SD 9.4; range 43.2-83.3)	55.5 (SD 13.8; range 22.1-80.1)	61.7 (SD 13.5; range 25.4-84.2)
Smoking at baseline	**No**	36 (90.0 %)	16 (94.1 %)	46 (88.5 %)	22 (88.0 %)
	Yes	4 (10.0 %)	1 (5.9 %)	6 (11.5 %)	3 (12.0 %)
Indication	**Conductive**	12 (30.0 %)	5 (29.4 %)	14 (26.9 %)	7 (28.0 %)
	Mixed	14 (35.0 %)	9 (52.9 %)	20 (38.5 %)	13 (52.0 %)
	SSD	13 (32.5 %)	2 (11.8 %)	17 (32.7 %)	4 (16.0 %)
	Other	1 (2.5 %)	1 (5.9 %)	1 (1.9 %)	1 (4.0 %)
Study site	**Nijmegen**	26 (65.0 %)	11 (64.7 %)	28 (53.8 %)	14 (56.0 %)
	Salford	7 (17.5 %)	4 (23.5 %)	12 (23.1 %)	6 (24.0 %)
	Göteborg	7 (17.5 %)	2 (11.8 %)	9 (17.3 %)	4 (16.0 %)
	Manchester	-	-	3 (5.8 %)	1 (4.0 %)

* 'Five-year follow-up population' includes all patients who were able to visit the clinic 5 years after implantation. 'Implant survival population' includes all patients from the original trial and was used to determine the implant survival/loss during the complete follow-up.

**The age at baseline was significantly different between the two treatment groups within the Five-year follow-up population (p=0.03). There were no other significant or important differences between groups.

ISQ

The ISQ values for the test implant were significantly higher compared to those of the control implant at all visits. The mean AUC for ISQ high between baseline and 5 years was 71.6 (SD ±2.0) and 66.7 (SD ±3.4) for the test and control implant, respectively (*p<0.0001*) (Figure 2). The corresponding values for ISQ low were 69.9 (SD ±2.0) and 64.9 (SD ±3.3) (*p<0.0001*).

Mean ISQ high at 5 years was 72.1 (SD ±2.2) for the test implant compared to 67.4 (SD ±4.0) for the control implant (*p<0.0001*). ISQ low resulted in similar results, with absolute numbers on average 1 to 2 points lower. An increase in ISQ values was recorded between the last visit at 3 years in the original trial and the 5-year visit in the current study for both implants. The change in ISQ high from baseline to 5 years was 2.03 (SD ±2.55, within group *p<0.0001*) for the test implant and 2.25 (SD ±4.95, within group *p=0.12*) for the control implant. No difference was noticed in increase from baseline between groups (*p=0.64*). All outcome variables are shown in more detail in Table 2.

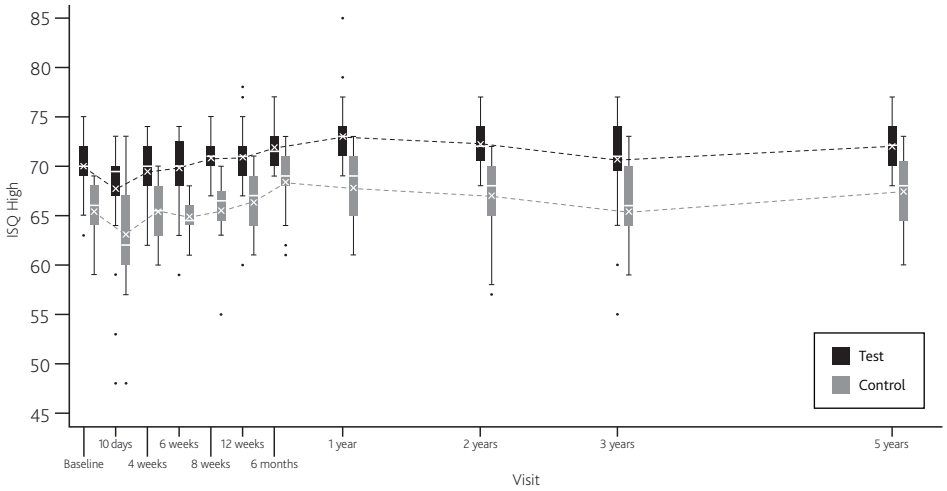

Figure 2. Box-and-whisker plot of ISQ high – Lines represent ISQ high for patients who attended the 5-year follow-up. Mean (cross) and median (horizontal line) are defined within the boxplot. The box represents the interquartile range, the whiskers the 95 % confidence interval and the single dots the outliers.

Soft tissue reactions

The classification of soft-tissue reactions using Holgers' index showed continued improvement for the test implant compared to the control implant, with less type 1 and type 2 soft-tissue reactions, as shown in Figure 4. At the 5-year follow-up visit, one patient (2.5 %) presented with a Holgers grade 2 in the test group, compared to four patients (23.5 %) in the control group (*p=0.048*). No patients presented with Holgers grade 3 or 4. The distribution of soft-tissue reactions over all Holgers grades (i.e. grade 0 to grade 4) was also significantly different between groups *(p=0.0013)*. When comparing the maximum severity of soft tissue reactions per patient across all visits (i.e. highest Holgers grade during complete study), a significant difference in favor of the test implant was also recorded (*p=0.015*) (Table 2).

Implant survival

In the test group, during the first three years of the study, one implant was explanted (chronic pain around abutment) and one implant was lost (eight weeks after surgery, at time of sound processor fitting, attributed to failure of osseointegration); in the control group no implants were explanted or lost during this period. Between the 3- and 5-year visits, another implant was lost in the test group (51 months after implantation). In the control group, one implant was explanted after 60 months and one implant was lost after 58 months (possibly related to radiotherapy at the implant site in the months prior to implant loss). Excluding explantations, the implant survival rate was 95.8 % and 95.0 % for the test and control group, respectively (Figure 3). The corresponding rates including explantations were 93.9 % and 90.0 %.

Table 2. Outcome variables

Outcome		Five-year follow-up population (n=57)		
		Test group (n=40)	**Control group (n=17)**	***Statistical analysis between groups***
ISQ AUC 0-5y*	**High**	71.6 (SD 2.0; range 65.6-75.8)	66.7 (SD 3.4; range 61.0-71.8)	*p<0.0001*
	Low	69.9 (SD 2.0; range 65.1-73.9)	64.9 (SD 3.3; range 58.3-70.1)	*p<0.0001*
ISQ at 5y	**High**	72.1 (SD 2.2; range 68-77)	67.4 (SD 4.0; range 60-73)	*p<0.0001*
	Low	70.9 (SD 2.3; range 66.0-75.0)	65.9 (SD 4.3; range 57.0-71.0)	*p<0.0001*
Change in ISQ 0-5y*	**High**	2.03 (SD 2.55; range -4-10)	2.25 (SD 4.95; range -7-11)	*p=0.64*
	Low	3.69 (SD 3.6; range-3-12)	4.06 (SD 4.89; range -5-13)	*P=0.59*
Holgers at 5y	**Grade 0**	36 (90 %)	9 (52.9 %)	
	Grade 1	3 (7.5 %)	4 (23.5 %)	
	Grade 2	1 (2.5 %)	4 (23.5 %)	
	Grade 3	0	0	
	Grade 4	0	0	*P=0.0013***
Maximum Holgers 0-5y*	**Grade 0**	10 (25 %)	2 (11.8 %)	
	Grade 1	22 (55 %)	5 (29.4 %)	
	Grade 2	7 (17.5 %)	9 (52.9 %)	
	Grade 3	1 (2.5 %)	1 (5.9 %)	
	Grade 4	0	0	*P=0.015***
Outcome		**Implant survival population (n=77)**		
		Test group (n=52)	**Control group (n=25)**	
Implant loss 0-5y*	**Including explantations**	3 (6.1 %)	2 (10 %)	
	Excluding explantations	2 (4.2 %)	1 (5 %)	

* 0-5y included all measurements from surgery till 5-year follow-up for ISQ, and all measurements from first postoperative visit till 5-year follow-up for soft tissue reactions.
** when comparing Holgers 0-1 with Holgers 2-4 statistical analysis between groups results in *p=0.048* for Holgers at 5y *and p=0.011* for maximum Holgers 0-5y.

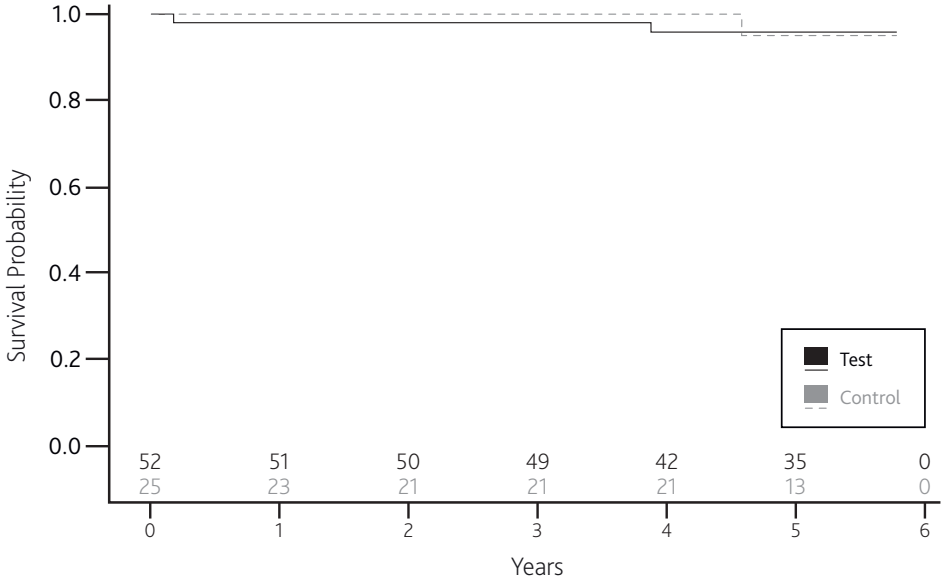

Figure 3. Implant survival, excluding explantations – Lines represent the survival curve for both study groups. Numbers above x-axis represent the numbers of patients at risk at the specific time point.

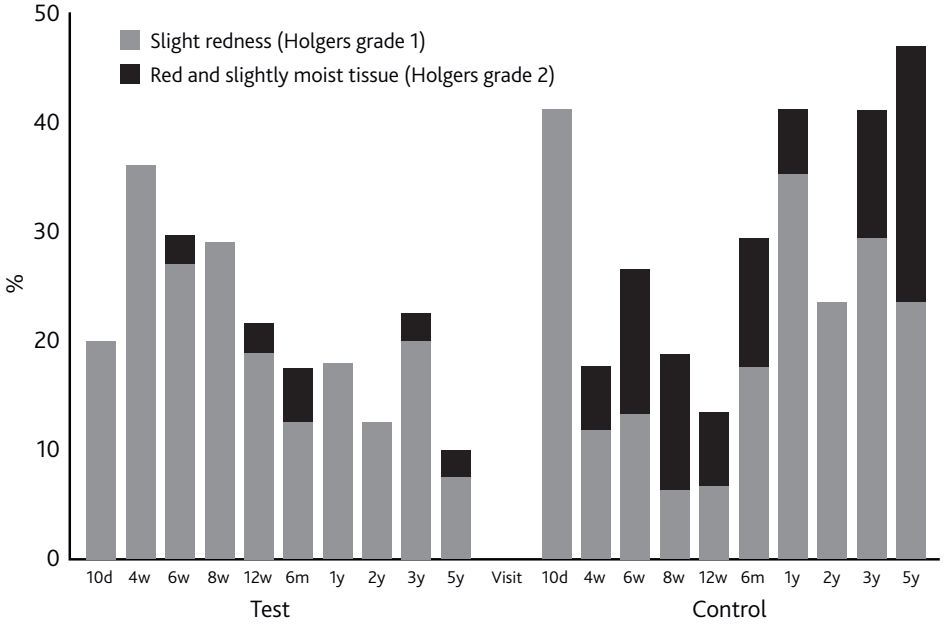

Figure 4. Soft tissue reactions according to Holger classification – Bars represent the percentage of patients with a soft tissue reaction in patients who attended the 5 year follow-up visit

Discussion

Principal findings

The aim of the current study was to compare clinical outcomes of a novel and a previous generation auditory osseointegrated implant system at long-term follow-up. The study showed superiority of the test implant compared to the control implant regarding ISQ measurements during the complete follow-up. The decrease in ISQ values recorded between 2 and 3 years of follow-up returned to higher ISQ values at the 5-year follow-up. The test implant continued to show superior soft tissue outcomes at 5 years, with less adverse soft tissue reactions in the test group. Implant survival of both study groups was slightly lower at 5 years of follow-up, however, still at high levels compared to previously reported numbers [10-12].

Strengths and limitations

The current investigation provides the first 5-year evidence on novel, wide implants in bone conduction hearing in a controlled approach. The original randomized controlled trial with multiple participating centers already provided very strong evidence for a high implant survival and good soft tissue outcome at 3-year follow-up. With the additional long-term follow-up in a prospective manner and with the original multicenter set-up, we were able confirm these good outcomes and showed reassuring results for future follow-up with increasing ISQ scores since last follow-up, continued high implant survival and good soft tissue outcomes for the test group.

One of the limitations of the current study is the loss to follow-up of some patients for the 5-year visit compared to the original study sample. Twenty patients, including five patients who had lost their implant or were explanted during the past five years and five patients who were already lost to follow-up/withdrew consent during the original trial, could not be included in the 5-year follow-up analysis of implant stability and soft tissue reactions. Consequently, a selection bias for this last follow-up visit cannot be excluded, even more since the current visit was a distinct investigation for which patients had to give separate informed consent. However, mostly minor differences in baseline characteristics between the five-year follow-up population and original study sample were observed. A difference in inclusion proportion between centers compared to the original trial and a small difference in age at baseline was noticed. All 77 patients of the original study population were included in the implant survival analysis; however, for the patients who could not be contacted, survival information was censored from a date prior to the 5-year follow-up and was based on patient files and/or information collected in the original investigation. The non-blinded follow-up and analysis is another limitation, as was already discussed in the previous reports [5,6].

Interpretation and comparison with other studies

The available literature reporting on the same type of implant generally shows good results in terms of implant stability and soft tissue outcomes; however, the majority of the investigations are retrospective cohort studies without a control group or small pilot studies [13,14,15-18]. For other wide auditory osseointegrated implants, similarly higher ISQ values compared to smaller diameter implants have been reported in short term follow-up [19]. To obtain more evidence on clinically important outcomes like implant survival, it would be highly desirable to have additional well-designed studies on wider implants in bone conduction hearing. Long-term follow-up, which was one of the major strengths of the current investigation, would be expedient for these studies.

Nelissen et al. previously hypothesized that the dip in mean ISQ between 2 and 3 years (for both types of implants) could be the result of marginal bone loss around the implant [6]. With the current results showing increasing values at the 5-year follow-up (with ISQ values comparable to the 2-year results), and with another investigation of the same implant showing no stability dip at 3 years any biological explanation of the previous decrease in stability seems unlikely [6]. An alternative reason for the dip could be a measurement error. Studies in dental implantology show conflicting results on intra-rater and inter-rater reliability of RFA [20-22]. Importantly, the small decrease detected by the stability measurements did not translate into clinical instability.

Implant stability as measured by RFA was chosen as the main outcome measure of the current study. This outcome measure should be interpreted with caution, as it is influenced by many factors in implant, abutment design and surgery [8]. It should additionally be emphasized that implant stability measures are a surrogate measure for implant survival, which is ultimately the most important for patients. Implant survival rates were shown to be high and equal for both study groups.

The implants in the present investigation were loaded with the sound processor from 6 weeks after surgery, which at the time of study initiation was not common practice. At that time, mostly loading protocols allowing 3 months of unloaded implants were reported. With the high implant survival rate and good soft tissue outcomes at 5 years, earlier loading seems to be safe at long-term follow-up. Nowadays even earlier loading is frequently reported and considered to be safe [23,24]. These early loading protocols allow patients to use their device as soon as possible with an improved patient satisfaction as a result.

Regarding one of the other secondary outcome measures, the decrease in soft tissue reactions is an important advantage of the new implant-abutment system. Percentages of adverse soft tissue reactions were reduced to 20 % for the new implant versus 58.8 % for the previous generation implant during the complete follow-up, representing an essential reduced need for post-operative treatment. Both the rounded shape of the abutment and the conical connection between the new implant and abutment that provides a tighter seal, have been proposed as explanations for this reduction [5, 6].

Conclusion

The new auditory osseointegrated implant design showed superiority compared to the previous implant design in terms of long-term implant stability as measured by resonance frequency analysis. Furthermore, although auditory osseointegrated implant surgery is a relatively safe procedure already, an important and persistent reduction in soft tissue reactions was noticed for the new implant. These good outcomes at longest follow-up reported to date in a prospective controlled study, support the replacement of the previous generation implants by the new BIA300 implant with abutment.

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chapter 6

Stability, survival, and tolerability of a 4.5-mm wide bone-anchored hearing implant: 6-month data from a randomized controlled clinical trial

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Objective To compare the stability, survival, and tolerability of two percutaneous osseointegrated titanium implants for bone conduction hearing: a 4.5-mm-diameter implant (test) and a 3.75-mm-diameter implant (control).

Methods Fifty-seven adult patients were included in this randomized controlled clinical trial. Sixty implants were allocated in a 2:1 (test–control) ratio. Follow-up visits were scheduled at 7, 14, 21, and 28 days; 6 and 12 weeks; and 6 months. At every visit, implant stability quotient (ISQ) values were recorded by means of resonance frequency analysis (RFA) and skin reactions were evaluated according to the Holgers classification. Implants were loaded with the bone conduction device at three weeks. Hearing-related quality of life was evaluated using the Abbreviated Profile of Hearing Aid Benefit (APHAB), the Glasgow Benefit Inventory (GBI), and the Glasgow Health Status Inventory (GHSI).

Results ISQ values were statistically significantly higher for the test implant compared to the control implant. No implants were lost and soft tissue reactions were comparable for both implants. Positive results were reported in the hearing-related quality of life questionnaires.

Conclusion These six-month results indicate that both implants and their corresponding hearing devices are safe options for hearing rehabilitation in patients with the appropriate indications. Loading at three weeks did not affect the stability of either implant.

Introduction

Percutaneous osseointegrated titanium implants have been used to attach vibrating bone conduction devices to the temporal bone since 1977 [1]. Both implants and devices, as well as the indications for application, have been studied extensively [2,3]. The clinical outcomes of these implants have been reported in large populations: long-term implant survival rates vary between 81.5% and 98.4%, while complications generally involve soft tissue inflammation [4-6]. Severe complications are rare [4,5].

Recently, the designs of these bone-anchored hearing implants have evolved to include wider diameters, based on the known advantages of wider implants in dentistry [7]. These 4.5-mm-diameter implants provide a larger contact surface between the implant and the bone compared to the 3.75-mm-diameter implants of the previous generation, which results in higher reported implant stability quotients (ISQ) and high implant survival rates [8,9]. Moreover, wider implants appear to have higher levels of initial stability, which allows for early loading of the implant with the device. Loading of these wider implants has been reported to be safe at three weeks after surgery [10].

The current randomized controlled clinical trial investigated ISQ, implant survival, and soft tissue tolerability of a new wider diameter implant in comparison to a previous generation implant in the first six months after implantation. Early loading of both implants was studied, with all implants loaded at three weeks. Subjective benefits of the bone conduction system were investigated using quality of life questionnaires.

Methods

Implants and patients

The test implant was the wide Ponto implant (diameter 4.5 mm, length 4 mm) and the control implant was the previous generation Ponto implant (diameter 3.75 mm, length 4 mm). Both implants used the same 6-mm abutment. The implants and abutments are developed and manufactured by Oticon Medical AB (Askim, Sweden) and are displayed in Figure 1.

Out of all of the patients indicated for a percutaneous bone conduction device, 57 adult patients with a total of 60 implants were consecutively included. Eligibility criteria were as follows: indication for a percutaneous implant; age of 18 years or older; bone thickness of at least 4 mm at the implant site; written informed consent given; abutment of 6 mm required (not longer); ability to participate in follow-up visits; no history of psychiatric diseases; no mental disabilities; no presumed doubt, for any reason, that the patient would not be able to attend all follow-up visits; no presence of diseases or use of treatments known to compromise bone quality at the implant site (e.g., radiotherapy, osteoporosis, diabetes mellitus).

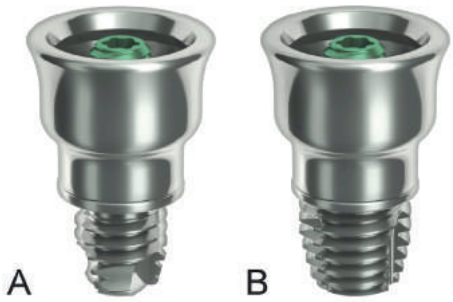

Figure 1. Control (a) and test (b) implants with abutments

Study design

The current study was designed as an open randomized controlled clinical trial in our tertiary referral center. The primary outcome parameter was implant stability measured as ISQ Low values in the first six months after implantation. Secondary objectives were to compare ISQ High values in the same period, ISQ Low and High values at all visits, time to stability dip (in ISQ Low) if applicable, implant survival, soft tissue reactions during all visits, and quality of life outcomes.

The sample size was based on the primary efficacy variable. A weighted average of ISQ Low values during the six-month follow-up period was obtained by the mean area under the curve (AUC) calculation using the trapezoid rule with all ISQ low measurements over the first six months. Data from a similarly designed previous study [11] were used for the sample size calculation. An expected difference of 4.5 in the mean AUC of the ISQ Low values of the test and the control groups, with unequal standard deviations (SDs) of ± 2.8 and ± 5.5, respectively, were used for determining the sample size. A two-sided *t*-test with Satterthwaite's correction for unequal variances was performed. For a power of 90%, significance level of 0.05, and randomization ratio of 2:1, a total of 60 implants needed to be included.

Randomization was performed in a 2:1 ratio (test-control). A computer-generated list of random allocations was used. The group assignments were enclosed in sequentially numbered opaque sealed envelopes. The randomization was blinded to the patients and investigators until the surgery was performed. Patients were allocated in consecutive order. Blinding of the investigators after the group assignments were made was not feasible because the appearances of the implants and instruments used during surgery were clearly different. Because most patients were operated under local anesthesia, the patients were also not blinded.

Implants and abutments were placed in a single-stage surgical procedure. The linear incision technique with subcutaneous tissue reduction was applied in all cases [12]. Implants were alternately placed within or posterior to the incision line. In accordance with the study

protocol, follow-up visits were scheduled at 7, 14, 21, and 28 days, 6 and 12 weeks, and 6 months. At each visit, resonance frequency analysis (RFA) was used to establish the ISQ. RFA uses magnetic pulses generated by the Osstell ISQ device (Osstell AB, Göteborg, Sweden) to excite the SmartPeg (type 55) that is connected to the abutment, which leads to vibration of the implant-abutment system. The intensity of these vibrations is analyzed by the device that computes the ISQ, which is an indication of the rigidity of the implant-bone link [13]. Perpendicular measurements result in an ISQ High value and an ISQ Low value. At each visit, the skin status was also assessed according to the Holgers classification [14]. Three weeks after surgery, the patients were fitted with the bone conduction device. The benefit of the bone conduction system was assessed using three questionnaires: the Abbreviated Profile of Hearing Aid Benefit (APHAB) [15], the Glasgow Benefit Inventory (GBI), and the Glasgow Health Status Inventory (GHSI)[16]. The APHAB and GHSI outcomes were only included in the analysis when both the baseline screening before implantation and the six-month evaluation had been completed. In cases where patients used hearing aids at the baseline evaluation, they were asked to complete the baseline questionnaire both for the aided and unaided conditions. The unaided condition was used as the baseline measurement for analyzing the benefit of the bone conduction system at six months.

Statistical analysis

Data management and statistical analyses were performed by external data managers and biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden) according to a predefined statistical analysis plan.

For comparisons between the test and control groups, Mann-Whitney *U* tests were used for all continuous variables, Mantel-Haenszel $\chi 2$ tests were used for all ordered categorical variables, Fisher's exact test was used for all dichotomous variables, and $\chi 2$ tests were used for all non-ordered categorical variables. For changes over time, Wilcoxon signed rank tests (continuous variables) and Sign tests (order categorical variables, dichotomous variables) were used. Groups were compared according to the intention-to-treat principle. For subjects lost to follow-up, last-observation-carried forward was used for ISQ measurements in the AUC calculations.

For implant variables, bilaterally implanted patients who received both a control and a test implant were included in both analyses. Patients who received two test or two control implants were represented by the mean of the two measurements for continuous variables or the worst value for categorical variables. For patient variables, bilaterally implanted patients who received both control and test implants were included in descriptive statistics but excluded in formal analyses on the patient level.

All tests were two-tailed with significance levels of 0.05 and were executed using SAS v9.2 and v9.3 software (SAS Institute Inc., Cary, NC, USA).

Ethical considerations

The clinical investigation was performed in accordance with the current version of the Declaration of Helsinki (Washington 2002, ISO 14155), Good Clinical Practice (International Conference on Harmonization Good Clinical Practice) and was approved by the local ethical committee.

Results

Patients

Fifty-seven patients with a total of 60 bone-anchored hearing implants (40 test and 20 control) were included in the randomization. Surgeries were performed between June 2012 and January 2014. Three patients received bilateral implants; two of these patients were randomized for both a test and a control implant, and one patient received two test implants. The baseline demographic information is shown in Table 1. No significant differences were found between the test and control populations. All randomized patients received their allocated treatment and could be included in the final six-month analysis.

Table 1. Patient demographics and baseline characteristics

Variable	Test (n=39)	Control (n=20)	p-value
Sex, n (%)			
Male	15 (38.5)	9 (45.0)	
Female	24 (61.5)	11 (55.0)	0.8554
Age in years, mean (SD)	53.7 (12.0)	53.0 (16.4)	0.4950
Smoking at baseline, n (%)	6 (15.4)	6 (30.0)	0.2750
Body mass index, mean (SD)	25.9 (4.2)	25.3 (4.1)	0.6029
Skin disease, n (%)	4 (10.5)	3 (14.3)	0.9176
Indication for bone-anchored hearing implant, n (%)			
Acquired conductive/mixed hearing loss	26 (66.7)	16 (80.0)	0.3657
Congenital conductive hearing loss	1 (2.6)	1 (5.0)	1.0000
Single-sided deafness	13 (33.3)	3 (15.0)	0.2704

Implant stability quotient

The mean AUC for ISQ Low was 64.4 (SD ± 2.9; range 55.5–70.1) for the test population (n = 39) and 59.3 (SD ± 2.1; range 55.5–62.5) for the control population (n = 20). The difference between groups of 5.1 ISQ points (95% CI 3.6–6.6; $p < 0.0001$) was statistically significant. For ISQ High, a difference of 3.3 (95% CI 1.8–4.7; $p < 0.0001$) was observed during the six-month follow-up, with a mean AUC of 65.8 (SD ± 2.7; range 57.0–70.5) for the test population and 62.5 (SD ± 2.8; range 56.9–66.8) for the control

population. At all follow-up visits, statistically significant differences in mean ISQs between both groups were recorded. The results are displayed in Figure 2. The mean increase in ISQ from baseline is statistically significant in both groups; however, the increase in ISQ from baseline for the test implant is statistically significantly stronger compared to the increase for the control implant. The ISQ dip at 42 days for the test implant can be ascribed to a single implant that displayed a very low ISQ (ISQ Low 46, ISQ High 52) but remained clinically stable and presented with an ISQ within the normal range at the next follow-up appointment.

No dip in mean ISQs was observed, as the ISQ High and ISQ Low values were higher than the baseline ISQ values (at surgery) at all follow-up visits.

Implants were loaded three weeks after surgery (with a two-day range) in all but one patient (loaded at 24 days). This early loading moment did not seem to influence ISQ values, as these progressed positively in both implants.

At six months, a mean increase in the ISQ Low from the time of surgery of 4.5 (SD ± 4.6; range –4–29) was observed for the total group (n = 59), which was significantly different from the ISQ low at the time of surgery ($p < 0.0001$). The mean increase was 5.1 (SD ± 4.9; range –4–29) in the test group and 3.3 (SD ± 3.8; range –3–13) in the control group. The mean difference in the increase in ISQ Low between both groups was statistically significant (95% CI –0.7–4.4; $p = 0.046$).

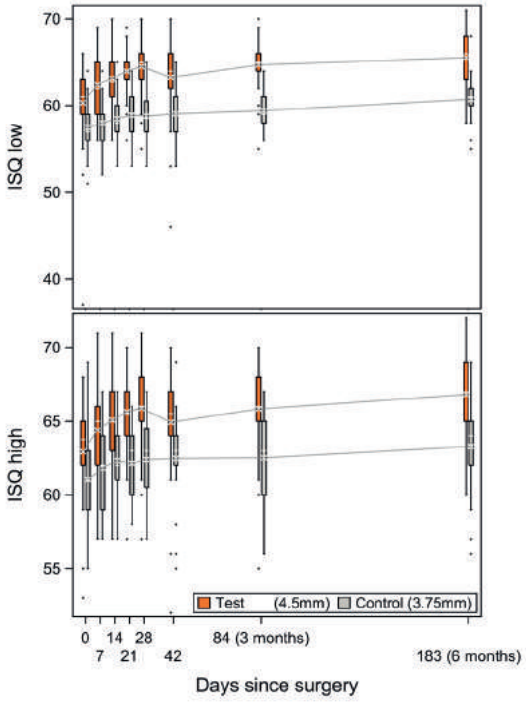

Figure 2. Box-and-whisker plots of ISQ low and ISQ high measurements. The mean (cross) and median (horizontal line) are defined within each box plot. Dots represent outlier values

Survival and tolerability

No implants were lost during the follow-up period. In each study group, one implant required surgical revision of the soft tissue. One patient who suffered from psoriasis presented with insufficient skin healing after surgery and the other patient presented with skin partially overgrowing the abutment. Three implants (7.7%) in the test group and two implants (10.0%) in the control group developed adverse skin reactions (Holgers grade 2–4). Results related to soft tissue reactions are displayed in Figure 3. The analysis of soft tissue statuses throughout the follow-up period revealed findings of Holgers grade 0 in 87.1 % (test) and 88.4 % (control) of visits, Holgers grade 1 in 11.8 % (test) and 9.5 % (control) of visits, Holgers grade 2 in 1.1 % (test) and 1.4 % (control) of visits, Holgers grade 3 in 0.0 % (test) and 0.7 % (control) of visits, and no Holgers grade 4 cases over all of the visits. Two out of the five patients who presented with adverse skin reactions suffered from skin diseases. Furthermore, no statistically significant differences were noted in other postoperative complications: bleeding or hematoma (one (2.6%) test patients versus one (4.8%) control patient), pain or numbness (four (10.5%) test patients versus two (9.5%) control patients), and wound dehiscence (three (7.7%) test patients versus two (10.0%) control patients). Additionally, skin height did not differ between the two groups.

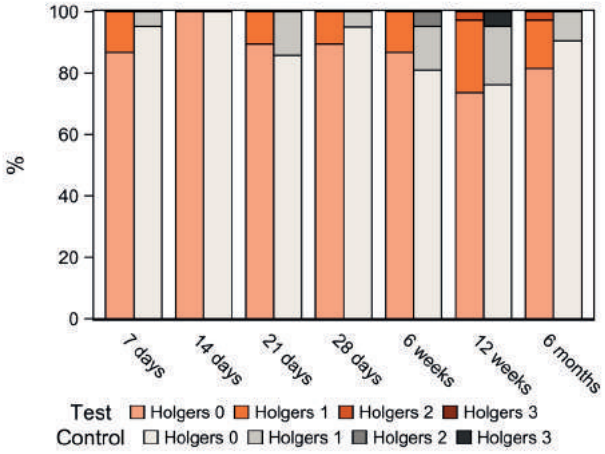

Figure 3. Soft tissue tolerability for test and control groups as a percentage of all visits according to the Holgers classification. Note that only Holgers grade 0–3 are depicted, as no Holgers grade 4 was observed

Quality of life

The GBI questionnaire was completed 12 weeks after surgery. Eight patients completed the questionnaire outside of the defined visit window (mean of 22 days after the planned visit date). These results were still included in the final analysis. No differences were observed in the outcomes between the test and control groups. The results are shown in Table 2.

Table 2. Subjective benefit as measured by the GBI

Variables (SD)	Test (n=39)	Control (n=20)	p-value
Total score	33.1 (20.0)	36.5 (14.1)	0.4889
General subscale	46.9 (25.5)	50.7 (21.2)	0.5715
Social subscale	11.0 (20.6)	10.0 (18.6)	0.9199
Physical subscale	1.28 (18.9)	6.67 (14.7)	0.0371

All patients completed the APHAB and GHSI questionnaires six months after surgery. However, five patients did not complete baseline questionnaires and were consequently excluded from the benefit analysis. One additional patient did not complete the baseline APHAB, while another three patients were excluded from the benefit analysis using the GHSI because of incomplete data on the six-month questionnaire. The outcomes of these questionnaires are displayed in Figure 4. For the GHSI, significant improvement was observed for the total and general scores, but not for the social and physical subscales. The APHAB indicated that there was statistically significant improvement on all of the subscales in the aided condition compared to the unaided condition.

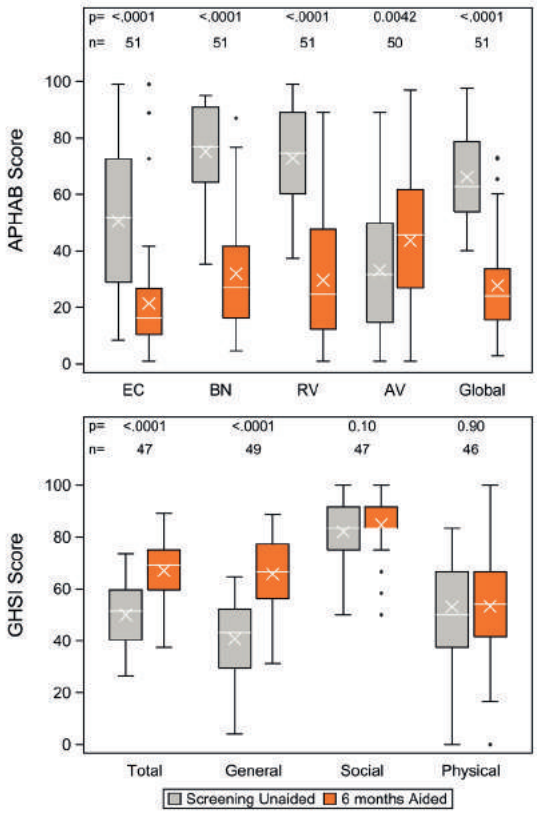

Figure 4. Subjective benefit as measured by the APHAB and GHSI questionnaires, completed before surgery and after 6 months of follow-up. The subscales of the APHAB are represented by the abbreviations on the x axis: EC ease of communication, BN background noise, RV reverberation, and AV aversiveness of sounds

Discussion

The current randomized controlled clinical trial compared outcomes of two percutaneous bone-anchored hearing implants for bone conduction devices with six months of follow-up. These implants, a new 4.5-mm-diameter implant (test) and the 3.75-mm previous generation implant (control), were both loaded with the bone conduction device at three weeks. The test implant exhibited significantly higher ISQ values than the control implant. All other clinical outcomes were comparable between the implants. Quality of life generally improved in the aided condition compared to before implantation.

The strengths of the current study include the absence of cases lost to follow-up and the conscientiously followed prospective study protocol. The tightly spaced follow-up visits allow for a detailed analysis of the development of the implant's stability. Therefore, the study design yielded useful information on short-term clinical results for both implants. The study's strength lies also in the fact that only a single parameter, the implant width/design, was varied. A limitation of the current study was the non-blinded follow-up for the investigators and patients.

Both implants exhibited positive trends in ISQ measurements that generally increased from baseline until the final follow-up at six months. These positive trends are an indication of a progression in implant stability over time. RFA application in bone anchored hearing implants has gained increasing interest in recent years. However, to date, reporting standards vary widely. Therefore, comparisons between different studies should be made very carefully. Foghsgaard and Caye-Thomasen [9] also studied the test implant and found an increasing trend in ISQ in the first year after surgery; however, they noted a slight decrease at the second follow-up visit (mean 7.3 weeks), when loading was applied. In our results, the ISQ was never lower than at surgery. It is worth noting not only that the test implant gave higher ISQ values on average, as expected, but also that the increase in ISQ over time was significantly higher for the test implant than the control implant. Although the present investigation was limited to adult patients with normal bone quality, it might be anticipated that the positive outcomes of the test implant could improve treatment outcomes in pediatric patients and patients with compromised bone quality. In comparable prospective studies on another wide implant type, increasing ISQ trends were reported in the first six months as well, with a dip in the ISQ at the first follow-up visit after surgery (ten days) [10,11]. A three-year follow-up on those implants revealed somewhat decreasing trends in ISQs beginning two years after implantation [8]. It will be interesting to extend the follow-up period of the current study to observe ISQ trends in comparison.

At this moment, the clinical implications of absolute ISQ values are not yet understood, so only trends should be evaluated. Additionally, in dental implantology, there is still a lack of studies documenting clear clinical benefits from therapeutic decisions based on RFA [13]. The large number of different implant designs in dental implantology might also influence this.

The implant survival rate was 100% for both implants. The same percentage was also reported for the current test implant in another one-year follow-up prospective case series [9]. An implant survival rate of 96.8% was reported on the current control implant in a retrospective case series with a mean follow-up period of 16.9 months (range 12.1–25.2 months) [17]. These survival rates are slightly higher than those reported in two other prospective studies on a different wide implant type [10,11]. Although all of these are short-term results, the first year after surgery has been reported to be critical, as more than half of implant losses occur in that year [4]. The current study will be extended to compare the results to long-term survival figures from retrospective analyses. Varying survival rates of 81.5% to 98.4% with maximum follow-up periods of up to 32.5 years have been reported on previous generation implants (3.75-mm diameter flange fixtures with a design comparable to that of the current control implant) [4-6].

Soft tissue tolerability was comparably good in both the test and control implants, with incidental adverse Holgers grade 2 and 3 skin reactions. This was expected because the abutment, which is believed to mainly influence the skin outcomes, was the same for both the test and control groups. The current adverse soft tissue events are comparable or even slightly better than rates reported from this center in the studies of another type of wide implant [10,11], also installed with skin thinning techniques. A remarkable fact is that two out of five patients who presented with adverse skin reactions suffered from skin diseases, which is a higher incidence than in the study population as a whole. This is in agreement with earlier observations [18,19] and the more recent identification of skin diseases as risk factors for skin reactions around bone-anchored hearing implants in a large retrospective cohort study [20].

As both implants were loaded at three weeks after implantation, the current study established that early loading did not affect the positive ISQ trend and shortterm clinical outcomes. This is confirmed by another study of the current control implant that reported on a loading time as early as two weeks after implantation [21]. Early loading of two, three and four weeks has also been studied on another type of wide implant with promising short-term results [10,22,23].

Hearing-related quality of life improved due to the system as a whole, as patients reported improvements on both the APHAB and GHSI questionnaires from pre-implantation to six months later. The aided APHAB outcome is comparable to a similar sized population with single-sided deafness fitted with bone conduction devices [24] and better than a larger population of elderly patients fitted with bone conduction devices for mixed indications [25]. The APHAB outcome can be strongly influenced by the sound processor used, with modern sound processors producing significantly better aided APHAB scores than older technologies [26]. To our knowledge, the GHSI has not been used to evaluate quality of life improvements with percutaneous bone conduction devices. GBI scores were also positive and comparable between groups. The current GBI outcome compares positively to other

studies that used the GBI to establish benefit from bone conduction systems (see Table 3 in Faber et al. [10]). It should be emphasized that indications and patient characteristics influence quality of life, so comparisons with these other studies should be made carefully. Intra-study comparisons of aided versus unaided conditions are therefore more important than inter-study comparisons.

Conclusion

After six months of follow-up, outcomes of a new 4.5-mm-diameter implant for bone conduction devices compared to the previous generation 3.75-mm-diameter implant exhibited higher ISQ values and similarly promising clinical characteristics. No implants were lost, and soft tissue tolerability was good. Loading both implants at three weeks appeared to be safe and hearing-related quality of life improved. These positive short-term results indicate that the new implant and its corresponding hearing devices loaded at three weeks is a safe option for hearing rehabilitation.

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chapter 7

Controlled clinical trial on bone-anchored hearing implants and a surgical technique with soft-tissue preservation

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Objective To compare the clinical and audiological outcome after linear incision with soft-tissue preservation and standard linear incision with soft-tissue reduction for placement of percutaneous bone-anchored hearing implants.

Study design Clinical trial with historical control-group from a prior randomized controlled trial.

Setting Tertiary referral center.

Patients and interventions Twenty-five patients were enrolled in a prospective cohort of bone-anchored hearing implant placement with linear incision and tissue preservation with a follow-up of 6 months. The control-group consisted of 25 patients from a prior randomized controlled trial in the same tertiary referral center. All sound processors were fitted 3 weeks after surgery.

Main outcome measures Numbness around the abutment, length of surgery, soft-tissue reactions according to Holgers' classification, Patient and Observer Scar Assessment Scale (POSAS), implant loss, Implant Stability Quotient (ISQ) and audiological outcome.

Results issue preservation resulted in better results on sensibility (mean percentage correct responses 98% (SD 4.4) versus 89% (SD 15.0), *p=0.003*), on the POSAS (mean observer score 15.3 (SD 4.3) versus 19.4 (SD 6.3), *p=0.006*), and shorter total surgery time (mean 24.6 minutes (SD 6.2) versus 31.9 minutes (SD 6.5), *p<0.001)*. More adverse soft-tissue reactions as measured by the Holgers classification were observed in the test-group (n=*7* (28%) versus n=1 (4%), *p=0.049)*. For ISQ and audiology the study did not provide evidence that tissue preservation is better or worse compared to tissue reduction.

Conclusions Tissue preservation compared to tissue reduction leads to a generally favorable clinical outcome, comparable audiology results and significantly shorter surgery time. Longer follow-up is warranted to conclude on the increased adverse soft-tissue reactions after 6 months.

Introduction

The surgical procedure for percutaneous titanium implants for bone conduction hearing has been modified several times since its introduction. During the last two decades there has been a tendency to less invasive surgery. When reviewing several frequently used techniques, the linear incision has been shown to be superior in several studies [1-3]. With the linear incision technique, as well as new implant and abutment designs, complications like implant loss and adverse soft-tissue reactions have decreased to 0-4% and 8-15% respectively per implant in the adult population [4,5].

In 2011 Hultcrantz described a modification of the linear technique, without soft-tissue reduction [6]. The rationale of soft-tissue preservation is less scar tissue formation, resulting in less numbness, cosmetic advantages and faster wound healing. Furthermore, tissue preservation results in shorter surgery times. This technique was shown superior on these matters in this study and consequently the preservation technique was adopted by many surgeons. However, most comparative studies use no or a less ideal control-group, including dermatome technique, or test-groups with a variation on the preservation technique, like a (modified) punch technique [6-13]. Additionally, audiological outcomes have not been reported thus far, while it has been mentioned that leaving the subcutaneous tissue around the abutment might dampen the vibrations to the skull [14].

The objective of the current study is to compare the aforementioned clinical and audiological outcomes uniformly after linear incision with soft-tissue preservation and a standard linear incision with soft-tissue reduction.

Methods

Study design and participants

The current study was set up as a clinical trial on soft-tissue preservation with a historical control-group in which soft-tissue reduction was applied. Twenty-five patients were consecutively included in the test-group. Patients were eligible to participate if they had an indication for a bone-anchored hearing implant, were 18 years or older and had no mental disability or psychiatric disease in medical history. We excluded patients with a bone thickness at implant site of less than 4mm, soft-tissue thickness of more than 10mm or inability to show up on all follow-up visits. We additionally excluded patients with diseases or treatments known to compromise bone quality at the implant site (e.g. radiotherapy, osteoporosis, diabetes mellitus).

The last 25 patients implanted with a wide implant using the linear incision technique with tissue reduction in a randomized controlled trial comparing wide implants with previous generation implants were asked to participate as controls in the current study [5]. Identical

implants and abutments were used in both groups and surgeries were performed by the same surgeons. Additionally, the same eligibility criteria were adhered to, with exception of the maximum soft-tissue thickness criterion.

Surgical techniques and follow-up

All patients were implanted with the Ponto wide implant (diameter 4.5mm, length 4mm, Oticon Medical AB, Askin, Sweden) during single-staged surgery. Abutment length was determined on soft-tissue thickness for the test-group (0.5-3mm: 6mm abutment, 3-6mm: 9mm abutment, 6-10mm: 12mm abutment). Follow-up visits were scheduled at 7 days, 21 days (sound processor fitting), 12 weeks, and 6 months. In the control-group, the standard linear incision technique, including tissue reduction and placement of a 6mm abutment, was applied in all cases [1]. Follow-up visits were scheduled at the same time points as the tissue preservation cohort, with additional follow-up at 14 days, 28 days, 6 weeks, and 12 months. Extra assessments, intended for the current study, were included at the 12-month follow-up visit for control patients.

Outcome measures

Primary outcome

The primary outcome measure was numbness around the abutment. Numbness was assessed with a broken wooden cotton swab; gnostic (cotton side) and vital (broken, sharp wooden side) sensibility were determined at 6 selected locations (Figure 1a) and percentages of correct answers were calculated. Subjective sensibility was additionally measured with a Visual Analogue Scale (VAS) from 0, no complaints, to 10, maximum numbness. Patients reported the area of subjective numbness as the diameter (centimeter) of skin with sensibility loss around the implant. Superiority of the tissue preservation technique was expected for the primary outcome variable.

Secondary outcomes

Secondary outcomes included length of surgery measured from start of incision to end of surgery collected from the electronic patient file. Surgery times were excluded when start or end of surgery was missing, or when a bilateral procedure or an additional procedure was executed in same setting.

Soft-tissue reactions were recorded according to Holgers' classification [15]. The Holgers' soft classification is scored on a 5-point scale from 0, no signs of soft-tissue reaction, to 4, an infection for which removal of implant is needed. Holgers grade 2 or higher was considered an adverse soft-tissue reaction in need of (local) treatment. Revision surgery (soft-tissue revision or abutment replacement) was recorded and skin height was assessed during follow-up. Skin height was related to the abutment using four different categories as shown in Figure 1b.

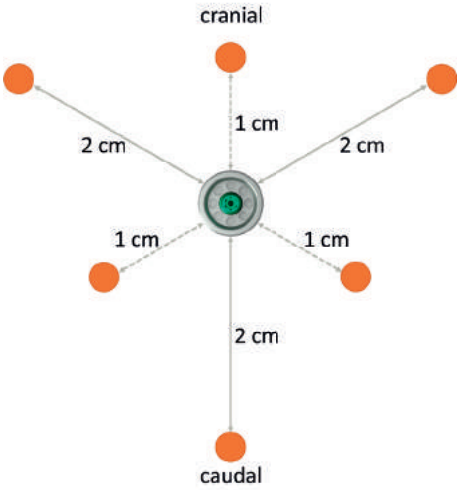

Figure 1a. Sensibility measurement locations, at all locations both gnostic (cotton side of wooden cotton swab) and vital sensibility (broken, sharp wooden side) will be tested randomly, the percentage correct answers was calculated for both as well as an overall percentage.

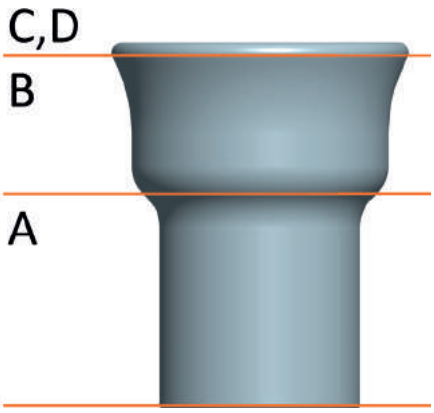

Figure 1b. Soft-tissue height relative to abutment (A under the shoulder of the abutment, B above the shoulder of the abutment, C partial overgrowth, D complete overgrowth).

Scar assessment with the Patient and Observer Scar Assessment Scale (POSAS) v2.0 was conducted [16]. The POSAS consists of a patient and an observer scale. Both scales contain 6 items with response options 1 to 10. Response option 1 corresponds to normal skin and 10 to worst imaginable. The total score range is from 6 to 60 for both scales. The patient and the observer additionally score their overall opinion (not included in the total scores).

Implant loss was recorded during follow-up and Implant Stability Quotient (ISQ) was measured at all visits using resonance frequency analysis (RFA) with the Osstell Mentor and a SmartPeg (type 55) (Osstell AB, Göteborg, Sweden). ISQ scores range from 0 to 100, with increasing scores displaying a more rigid implant-bone interface, but the score is also an representation of implant variables like implant diameter and abutment length [17]. Longer abutments will result in lower absolute ISQ scores at baseline, so in the current study, trends are compared between different abutment lengths [18]. Perpendicular measurements of the implant resulted in an ISQ high and an ISQ low value.

Furthermore, audiometric thresholds were collected. Bone conduction (BC) in situ thresholds were measured with the patients' sound processor on abutment and on a softband, additionally, BC thresholds were measured with a B71 transducer and audiometer (all measurements at a position 2cm cranial of the abutment).

Subjective benefit was measured by the Glasgow Benefit Inventory (GBI), the Glasgow Health Status Inventory (GHSI), the Abbreviated Profile of Hearing Aid Benefit (APHAB) questionnaires [19,20]. The GBI is an 18-item questionnaire, which evaluates the patients' perceived benefit from an otorhinolaryngology intervention [19]. Response options are on a 5-point Likert scale ranging from large improvement to large deterioration in health status. Total scores range from -100 (maximal adverse effect), 0 (no effect), to 100 (maximal positive effect). The GHSI measures the effect of a health problem on the quality of life of a person at the time the questionnaire is completed. The questionnaire contains 18 items and response options on a 5-point Likert scale. Total scoring is from 0 to +100, with higher scores indicating better health status. The APHAB is a 24-item inventory, scored in four 6-item subscales on communication abilities or perception of sound in daily life situations [20]. All items are scored on a 7-point scale indicating frequency of problems experienced. An average unaided an aided score is calculated ranging from 1 to 99, with higher scores indicating more problems.

The numbness assessment, POSAS scale and audiometric thresholds were collected in the test-group at 6 months and in the control-group at 12 months. This was required because control patients already passed their 6 months visit before start of the current study. All other outcome measures were collected at same time points in the test and the control-group. Outcome assessment was not blinded.

Sample size and statistical analysis

No sample size calculations were made; investigators' experience and practically feasible number of patients determined the sample size. For comparison between test-group and the control-group Fishers nonparametric permutation test was used for numbness variables, Mann-Whitney U-test was used for other continuous variables, Mantel-Haenszel chi-square test for ordered categorical variables and Fisher's exact test for dichotomous variables. For analysis over time Wilcoxon Signed rank test was used for continuous variables. Nonparametric methods were chosen on non-normality assumptions and small sample sizes. Missing values were not imputed and no adjustments were made for multiple testing. In addition to the intention to treat analysis, we also performed a post-hoc per-protocol analysis on numbness and POSAS, excluding a patient in the control-group who had previous bone-implant surgery with tissue reduction. The test and control-groups had a different number of visits, thus for analysis including visit-based data, only data from follow-up visits available for both groups were included, for cumulative variables all visits including extra visits were included. All tests were two-tailed with significance levels of 0.05. Analyses were performed using SAS v9.4 (Cary, NC). Data management and statistical analysis were performed by external data managers and biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden) according to a predefined statistical analysis plan.

Ethical considerations

The clinical investigation was performed in accordance with the current version of the declaration of Helsinki (Washington 2002, ISO 14155) and was approved by the local ethical committee. The current study was registered with ClinicalTrials.gov and assigned the identifier NCT02064478.

Results

Patient and surgery characteristics

All surgeries were performed between February 2014 and August 2014 in the test-group, and between March 2013 and January 2014 in the control-group. No patients were excluded in the test-group because of the additional skin thickness criterion. Baseline characteristics were similar between the two study groups (Table 1).

Table 1. Baseline characteristics

Characteristics	Preservation group (n=25)	Reduction group (n=25)
Sex, - n (%)		
Male	15 (60%)	10 (40%)
Female	10 (40%)	15 (60.0)
Age, yr - mean (SD)	51.5 (13.4)	53.9 (12.2)
Smoking at baseline, - n (%)	4 (16%)	4 (16%)
BMI at baseline, kg/m2 - mean (SD)	26.0 (3.9)	26.5 (4.2)
Skin disease at baseline, - n (%)	1 (4%)	3 (12%)
Indication, - n (%)		
Acquired conductive/mixed	21 (84%)	18 (72%)
Congenital conductive	1 (4%)	0 (0%)
SSD	3 (12%)	7 (28%)
Abutment length selected, - n (%)		
6mm	0 (0%)	25 (100%)
9mm	17 (68%)	0 (0%)
12mm	8 (32%)	0 (0%)

* There were no significant differences in baseline characteristics between the two study groups

Numbness assessment

The cotton swab numbness assessment resulted in a mean percentage of correct responses of 98% (SD 4.4) and 89% (SD 15.0) in the test and control group respectively (*p=0.003).* The subjective numbness assessment with the VAS score resulted in a mean VAS of 0.4 (SD 1.1) in the test-group and 1.7 (SD 2.4) in the control-group (*p=0.051).* The per protocol analysis showed similar results for all comparisons (Table 2).

Table 2. Primary and secondary outcome measures

Outcome		Preservation group (n=25) mean (SD)	Reduction group (n=25) mean (SD)	p-value
Numbness at 6/12 months *	**Gnostic sensibility, %**	96.7 (8.3)	88.7 (18.5)	*p=0.053*
	Vital sensibility, %	99.3 (3.3)	89.3 (17.9)	*p=0.007*
	Total sensibility , %	98.0 (4.4)	89.0 (15.0)	*p=0.003*
	Subjective numbness, VAS	0.36 (1.10)	1.69 (2.44)	*p=0.051*
	Area of subjective numbness, cm	0.24 (0.83)	0.89 (1.39)	*p=0.021*
Length of surgery, min	**Electronic patient file****	24.6 (6.2)	31.9 (6.5)	*p<0.001*
	Knife time	20.8 (4.3)		
Maximum Holgers across all visits 0-6m, – n (%)	**Grade 0**	11 (44%)	12 (48%)	
	Grade 1	7 (28%)	12 (48%)	
	Grade 2	4 (16%)	1 (4%)	
	Grade 3	3 (12%)	0 (0%)	
	Grade 4	0 (0%)	0 (0%)	*P=0.14*
Mild versus adverse soft tissue reactions	**Grade 0-1**	18 (72%)	24 (96%)	
	Grade 2-4	7 (28%)	1 (4%)	*P=0.049*
Skin height at 6 months	**A – under shoulder**	18 (72%)	17 (68%)	
	B – above shoulder	7 (28%)	8 (32%)	
	C – partial overgrowth	0 (0%)	0 (0%)	
	D – complete overgrowth	0 (0%)	0 (0%)	*P=1.00*
POSAS at 6/12 months * **	**P – Pain**	2.72 (1.77)	2.44 (1.96)	*p=0.41*
	P – Itching	2.48 (2.10)	2.84 (2.53)	*p=0.79*
	P – Color	2.88 (2.15)	3.88 (2.51)	*p=0.14*
	P – Stiffness	2.64 (2.08)	2.60 (1.80)	*p=0.98*
	P – Thickness	2.76 (2.70)	3.48 (2.20)	*p=0.067*
	P – Irregularity	2.36 (2.25)	3.64 (2.20)	*p=0.017*
	P– Total score	15.8 (10.8)	18.9 (9.7)	*P=0.11*
	P– Overall opinion	2.44 (2.31)	3.36 (1.87)	*p=0.014*
	O – Vascularity	2.88 (1.30)	3.64 (1.25)	*p=0.010*
	O – Pigmentation	2.16 (0.55)	2.76 (1.16)	*p=0.048*
	O– Thickness	2.92 (1.63)	3.32 (1.63)	*p=0.26*
	O – Relief	2.84 (1.28)	3.56 (1.53)	*p=0.048*
	O – Pliability	2.20 (0.50)	2.76 (1.23)	*p=0.092*
	O – Surface	2.28 (0.68)	3.32 (1.31)	*p<0.001*
	O – Total score	15.3 (4.3)	19.4 (6.3)	*p=0.006*
	O – Overall opinion	2.84 (1.21)	3.76 (1.30)	*p=0.006*

Table 2. Primary and secondary outcome measures (continued)

Outcome		Preservation group (n=25) mean (SD)	Reduction group (n=25) mean (SD)	p-value
ISQ low	**Baseline**	54.4 (3.5)	61.0 (3.4)	*p<0.001*
	AUC 0-6 months	57.0 (4.1)	64.2 (3.1)	*p<0.001*
	Change in ISQ 0-6mo	+4.6 (2.0)	+4.4 (3.2)	*p=0.86*
BC in situ at 6/12 months, dB	**Abutment, 250Hz-8kHz**	25.5 (12.8)	25.0 (11.8)	*p=0.93*
	Testband, 250Hz-8kHz	37.8 (11.3)	35.5 (10.0)	*P=0.53*
	B71, 250 – 4kHz	22.4 (11.2)	20.9 (11.7)	*P=0.79*
	Abutment – testband, 250Hz-8kHz	-12.2 (7.0)	-10.5 (4.7)	*p=0.10*
	Abutment - B71, 250 – 4kHz	-0.99 (4.86)	-0.48 (4.72)	*p=0.79*

*Intention to treat analysis is presented. Slightly different results are shown for per protocol analysis in the control group. Gnostic: mean control group 88.2 (SD 18.7), p=0.044. Vital: 88.9(18.2), p=0.003. Total: 88.5 (15.1), p=0.002. Subjective: 1.76 (2.47), p=0.039. Area of subjective: 0.93 (1.41), p=0.016.
** n=20 for test group and n=22 for control group
***Intention to treat analysis is presented. Slightly different results are shown for per protocol analysis in the control group. Largest differences were seen for the patient scale on stiffness (mean 2.46 (SD 1.69), p=0.87), and for the observer scale on pliability (2.63 (1.06), p=0.14), surface (3.21 (1.22), p=0.002) and relief (3.46 (1.47), p=0.071). On total scores this resulted in 18.5(9.6) for the patient scale and 19.0 (6.2) for the observer scale

Length of surgery

The mean surgical time as registered in the electronic patient file was 24.6 minutes (SD 6.2; range 13-39) in the test-group and 31.9 minutes (SD 6.5; range 20-44) for the control-group (*p<0.001).* In the test-group the length of surgery was also recorded as knife time only (measured by the investigator), resulting in 20.8 minutes (SD 4.3; range 13-29).

Adverse events

In the test-group device/surgery-related adverse events included one patient with fever in the first days postoperative without any local signs of infection, one patient with persistent itch around the abutment and one patient with ongoing pain around the abutment (not able to get sound processor on abutment, different sound processor selected). In the control-group related events included two patients with a wound dehiscence at 7 days, two patients with mild pain around the abutment, one patient with scar hypertrophy and one patient with an abscess next to the abutment (required recurrent incision and antibiotic treatment).

For the test-group 7 patients required one additional unplanned visit, in the control-group two patients required one unplanned visit and one patient required 4 unplanned visits (patient with abscess).

Other soft-tissue outcomes

Soft-tissue reactions

In both groups no Holgers grade 4 reactions were recorded. Comparing all Holgers grades as maximum per implant across all visits between groups, no significant difference was found (*p=0.14)*. When comparing clinically relevant adverse reactions (Holgers ≥2), 28% (n=7) adverse reactions in the test-group versus 4% (n=1) in the control-group were observed (*p =0.049)*. The rate of adverse soft-tissue reactions per visit was 7.5% (n=8 in 282 visits, one patient with two adverse soft-tissue reactions) and 0.6% (n=1 in 356 visits). All adverse soft-tissue reactions resolved after one or two local treatment regimens.

Revision surgery & skin height

One revision surgery was performed in the control-group one month after initial surgery because of high skin. No partial or complete soft-tissue overgrowth was observed, and no differences between groups were noticed in skin height during first 6 months.

POSAS

On the patient scale highest values were scored for color, thickness and irregularity. Differences between groups were noted on irregularity and on overall opinion. The mean total score for the patient scale was 15.8 (SD 10.8) for the test-group versus 18.9 (SD 9.7) for the control-group (*p=0.11*). On the observer scale highest values were scored for vascularity, thickness and relief. Differences between groups were noticed in vascularity, pigmentation, surface and overall opinion. The mean total observer score was 15.3 (SD 4.3) for the test-group versus 19.4 (SD 6.3) for the control-group (*p=0.006*). The per protocol analysis showed similar results (Table 2).

Implant loss and ISQ

No implants were lost in either group. ISQ low was higher at baseline (surgery) in the control-group (*p<0.001*), as was expected with longer abutments in the test-group, and remained higher during follow-up (AUC ISQ low 0-6 months, *p<0.001*). Nevertheless, no difference between groups was recorded in the change of ISQ from surgery. ISQ low showed a mean increase of +4.6 (SD 2.0) in the test-group and +4.4 (SD 3.2) in the control-group (change within groups *p<0.001*; difference between groups *p=0.86)*. ISQ high showed similar results, with absolute numbers 1 to 2 points higher on average and slightly less increase over time (Figure 2b).

Audiology

The overall thresholds at 250Hz to 8kHz on testband and at 250Hz to 4kHz on B71 showed no differences between groups, indicating similar hearing thresholds. The overall

thresholds on abutment, which are clinically most relevant given similar hearing thresholds, showed no difference between groups (mean 25.5 (SD 12.8) versus 25.0 (SD 11.8), *p=0.93)*. Additionally, the overall difference between abutment and testband (250Hz to 8kHz) showed no difference between test and control-group (mean -12.2 (SD 7.0) versus -10.5 (SD 4.7), (*p=0.10*).

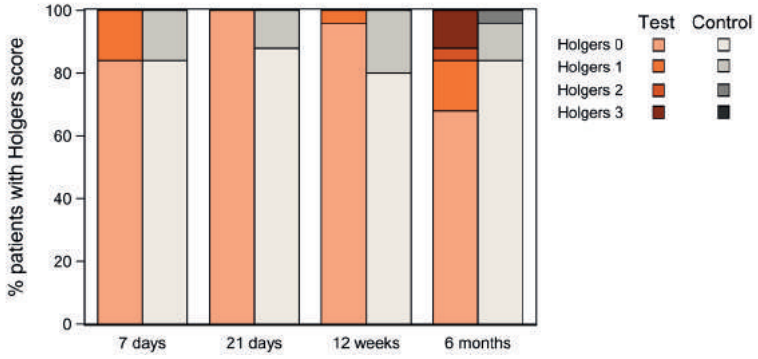

Figure 2a. Soft-tissue reactions according to Holgers' classification, as a percentage per visit per study group, not including extra visits.

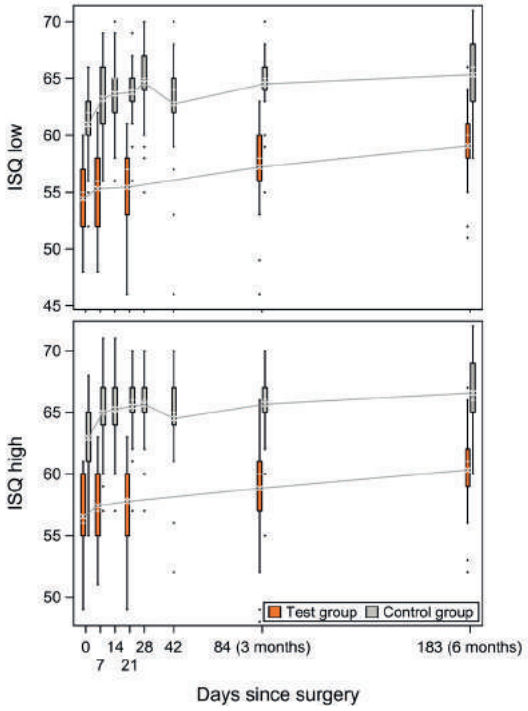

Figure 2b. Box-and-whisker plots of ISQ low and ISQ high measurements over time. The mean (cross) and median (horizontal bar) are defined within each plot, boxes represent interquartile range, whiskers represent 95% range and dots represent outlier values.

Comparing individual frequency thresholds between the two study groups for the abutment and for the B71 conditions, no significant differences where noticed. In the testband condition a difference was noted at the 1 kHz frequency (mean 30.2 (SD 12.9) versus 20.8 (SD 14.0), *p=0.028*). Additionally, comparisons between different conditions on individual frequencies were performed. For comparison between test and control-group when looking at the difference between abutment and testband, a significant difference was noticed at 1kHz (mean -14.4 (SD 7.8) versus -5.0 (SD 7.2), *p<0.001)* and 1.5kHz frequency (mean -9.6 (SD 7.1) versus -5.4 (SD 6.8), *p=0.037)*. When comparing abutment to B71 conditions, a difference was observed on the 1.5kHz situation (mean -5.8 (SD 5.5) versus -2.0 (SD 7.8), *p=0.044)*. All mean thresholds per frequency are shown in Table 3.

Table 3. BC direct thresholds on abutment, testband and B71 – mean (SD), preservation n=25, reduction n=25.

	250Hz		500 Hz		750 Hz		1000 Hz		1500 Hz		2000 Hz		3000 Hz		4000 Hz		6000 Hz		8000 Hz	
	P	R	P	R	P	R	P	R	P	R	P	R	P	R	P	R	P	R	P	R
Abutment	11.6 (11.2)	8.4 (10.1)	13.8 (10.4)	14.2 (10.5)	13.8 (12.4)	12.2 (11.7)	15.8 (13.0)	15.8 (12.2)	17.0 (15.5)	18.6 (17.8)	29.0 (14.8)	25.6 (16.2)	32.8 (16.7)	32.8 (21.3)	37.4 (19.5)	36.0 (20.1)	40.2 (21.5)	40.6 (20.7)	44.0 (24.0)	46.0 (19.9)
Testband	10.0 (11.3)	7.6 (9.8)	20.6 (10.2)	16.8 (12.8)	27.4 (14.9)	26.6 (11.6)	30.2 (12.9)	20.8 (14.0)	26.6 (15.5)	24.0 (17.8)	41.4 (15.4)	37.2 (18.3)	48.4 (16.5)	48.6 (16.6)	51.2 (14.6)	53.2 (14.7)	61.6 (14.6)	57.4 (13.1)	61.9 (15.4)	62.8 (10.8)
B71	7.4 (12.0)	7.8 (11.7)	14.0 (11.2)	12.0 (12.1)	17.6 (13.4)	14.4 (12.9)	17.0 (12.6)	16.6 (13.0)	22.8 (14.5)	20.6 (17.0)	31.8 (16.0)	27.2 (16.8)	35.7 (16.5)	36.0 (20.1)	32.8 (17.9)	32.8 (22.4)				

P= Preservation group, R=Reduction group.
Selected sound processor for the test group: Ponto pro n=0, Ponto pro power n=2, Ponto plus n=5, Ponto plus power n=18.
For the control group: Ponto pro n=4, Ponto pro power n=16, Ponto plus n=2, Ponto plus power n=3.

Health related quality of life

The GBI was completed 12 weeks after surgery. The GBI showed a positive result (>0) in 98% of all 50 patients on the total score (mean total score 32.3, SD 19.9, range -6.3 to 88.9). On the general subscale 96% of patients scored positively. The social and physical subscale showed a neutral effect in most patients, 75% respectively 74%, and a considerable proportion with a positive result, 25% resp.18%.

The GHSI and APHAB were both assessed at 6 months. For the GHSI total score baseline (best score, either aided or unaided) to visit at month 6 (aided) a significant mean

improvement of +12.4 (SD 10.5; *p<0.0001*) was observed. For the general score also an improvement was observed, the social and physical scores did not show a improvement or deterioration. For the APHAB questionnaire an improvement was noted on the mean total score at 6 months compared to best baseline score of -24.3 (SD 23.1; p<0.0001). This difference was observed on all subscales with exception of the aversiveness scale (Figure 3).

No significant differences were found between test and control-group in GBI results or benefit on the GHSI and APHAB.

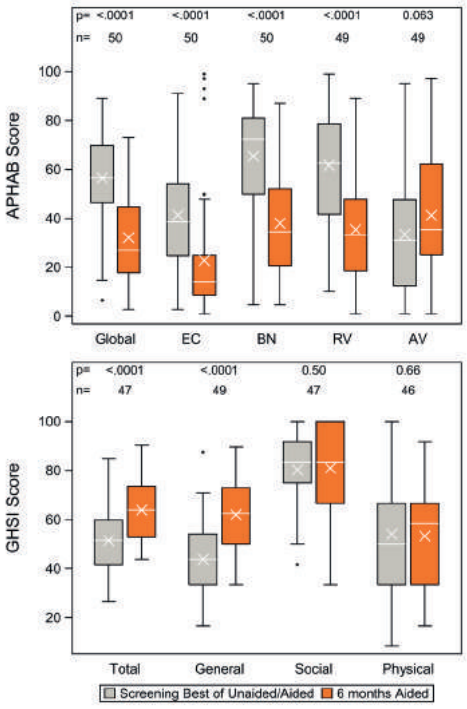

Figure 3. Health related quality of life measured by the GHSI and APHAB questionnaires, completed before surgery (best score, either aided or unaided) and after 6 months (aided) (EC ease of communication, BN background noise, RV reverberation, AV aversiveness). The mean (cross) and median (horizontal bar) are defined within each plot, boxes represent interquartile range, whiskers represent 95% range and dots represent outlier values.

Discussion

Key findings

Tissue preservation surgery resulted in better results on sensibility and POSAS scar assessment scale and shorter surgery time. However, significantly more adverse soft-tissue reactions according to the Holgers score were observed. For ISQ and audiology the study did not provide evidence that tissue preservation is better or worse compared to tissue reduction.

Strengths and limitations

One of the important strengths of the current study is the selection of the control-group with a standard linear incision with tissue reduction. All studies performed so far use no or a less ideal control-group, consequently superiority of the new technique over the current gold standard could not be concluded on these studies [6-9,12]. Aside from the selection of the control-group, the current study adds important results on audiological outcomes.

By taking the control patients from a previous trial, the interventions could not be randomized and follow-up visits were separated in time for the two study groups. The 12-month evaluation of the control-group was, however, expected to result in better outcomes on sensibility and POSAS for the control-group, since healing of soft-tissue would be more complete at longer follow-up. We feel that the benefit of fewer patients needed for participation and earlier availability of results outweigh the drawbacks of the selected study design. Moreover, both groups were included with the same eligibility criteria and had comparable baseline characteristics.

Follow-up visits were more tightly spaced in the control-group. It might be possible that more frequent visits to the out-patient clinic result in better soft-tissue care. Conversely, more than half of adverse soft-tissue reactions were noticed at 6 months and the more tightly spaced visits were completed in the first 6 weeks.

Another limitation could be the non-blinded follow-up. However, since both surgical techniques result in different appearance of implant sites and abutment lengths, with accompanying ISQ values, blinding of observers and patients would not be feasible.

Interpretation

For the primary outcome variable numbness, we recorded significant differences in favor of the tissue preservation technique, though in most patients treated with standard linear incision technique also good sensibility scores of > 90%, and low VAS scores with small areas of subjective numbness were observed. Additionally, several patients reported difficulties answering the questions on this scale due to limited visibility, especially on the color and overall question. Moreover, patients reported limited importance of both VAS and area of numbness and appearance of the scar behind the ear during evaluation with the POSAS. This might though be biased by the short follow-up and dominated patients' perspectives by the good outcomes on hearing improvement.

The difference in absolute ISQ scores at baseline and during follow-up can be explained by different abutment lengths [18]. Since trends in ISQ during follow-up showed a similar development, no evidence of stability differences is suggested by these data. The increased soft tissue reactions should be interpreted with care, and further follow-up is needed to draw conclusions. The number of adverse soft-tissue reactions in the control-group (n=1, 4%), was lower compared to the percentage of adverse soft-tissue reactions in the complete study group from which the current control-group was a subset [5]. A pathophysiological hypothesis

for the increased soft-tissue reactions could be the result of more free movement of soft-tissue surrounding the abutment, as was described previously by Brånemark and Albrektsson [21].

All implants were loaded with a sound processor 3 weeks after surgery. The current good results suggest that loading at 3 weeks seems to be safe at short-term follow-up, also when using tissue preservation and longer abutments. The literature supports these early loading protocols with even longer follow-up and similar good outcomes in the standard linear incision technique [22,23].

Comparing audiological outcomes by BC in situ measurements, we noticed only minor differences in thresholds between both groups, except for testband at 1kHz and difference between abutment-B71 at 1.5kHz and abutment-testband on 1kHz and 1.5kHz. The significantly poorer results on these frequencies for the test-group may be due to changes in resonance frequency of the sound processor in the transcutaneous conditions, resulting in less output in the mid frequencies [14]. This effect is most strongly present in cases with tissue preservation. Nevertheless, it seems that surrounding skin around abutments and longer abutments did not affect the transmission of sound at 6 months follow-up with current set-up.

Generalizability and conclusions

This study adds knowledge in the rapidly evolving tissue preservation trend in bone anchored hearing implant surgery. Since we noticed some conflicting results compared to the existing literature, like the increase in soft-tissue reactions according to Holgers, this study emphasizes the need for a more elaborate evaluation of new surgical techniques before complete substitution of currently applied methods is sensible.

Based on the current 6 months results, the overall difference between these surgical techniques from a patient's perspective might not be evidently in favor of either tissue preservation or tissue reduction: comparable results on audiology, less numbness and better POSAS scores, yet more soft-tissue reactions according to Holgers were recorded in the first 6 months. However, since adverse soft-tissue reactions in the study completely recovered after one or two local treatment regimens, the burden for patients might be relatively minor. An additional important gain is the reduction of surgery times.

Longer follow-up of the current study will be needed to draw firm conclusions, especially regarding soft-tissue reactions. Data on 36 months results will be reported for this study later.

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chapter 8

Audiological and clinical outcomes of a transcutaneous bone conduction hearing implant: 6-month results from a multicenter study

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Objectives To compare the hearing performance of patients with conductive and mild mixed hearing loss and single-sided sensorineural deafness provided with a new transcutaneous bone conduction hearing implant (the Baha Attract System) with unaided hearing as well as aided with a sound processor on a softband. Furthermore, to evaluate safety and subjective benefit before and after implantation of the test device.

Participants Fifty-four adult patients in five participating centres were enrolled in this prospective study. Baseline data were collected during a preoperative visit and after a softband trial all patients were implanted unilaterally. Follow-up visits were scheduled at 10 days, 4 weeks, 6 weeks, 12 weeks, and 6 months.

Main outcome measures Free-field hearing thresholds (PTA4 in dB HL; mean threshold at 500, 1000, 2000, 4000Hz) (primary outcome measure). Individual free-field hearing thresholds, speech recognition in quiet and in noise, soft tissue status during follow-up and subjective benefit as measured with the APHAB, SSQ and HUI questionnaires.

Results

Implantation of the Baha Attract System resulted in favourable audiological outcomes compared to unaided conditions. On the primary outcome parameter, a statistically significant improvement was observed compared to unaided hearing for the patients with conductive/mixed hearing loss (mean PTA4 difference -20.8dB HL, SD 9.8; *p<0.0001),* and for the patients with single-sided sensorineural deafness (SSD) (mean PTA4 difference -21.6dB HL, SD 12.2; *p<0.0001).* During all audiology tests, the non-test ear was blocked. Statistically significant improvements were also recorded in speech tests in quiet and noise compared to unaided hearing for the conductive/mixed hearing loss group and for speech in quiet in the SSD group. Compared to the preoperative measurement with softband, no significant differences were recorded in the PTA4 free-field hearing threshold or the other audiological outcomes in either of the groups (p>0.05). Soft tissue related issues observed during follow-up included numbness, pain/discomfort at the implant site and to a lesser extent pressure related skin complications. A declining trend was noted in the rate of these complications during follow-up. Approximately 20% of patients reported some degree of numbness and 38% (slight) pain/discomfort at final follow-up of 6 months. Good results on the subjective benefit questionnaires were observed, with statistically significant improvements on APHAB and SSQ questionnaires, and on the hearing attribute of HUI3.

Conclusions

The Baha Attract System provided a significant improvement in hearing performance and subjective benefit compared to the preoperative unaided condition (with the non-test ear blocked). Hearing performance of the Baha Attract was similar to a test situation with the same sound processor on a softband. A proportion of the patients reported numbness and pain/discomfort at the implant site during follow-up, especially during the first postoperative weeks. Based on the results of the current multicentre study, the Baha Attract can be considered as a treatment option for patients with the aforementioned hearing losses. Especially in the SSD patients a careful selection procedure is warranted. Therefore a pre-operative trial should be part of the decision making process before fitting a patient with the Baha Attract System.

Introduction

Bone conduction hearing implant systems (also referred to as auditory osseointegrated implant systems) have been used for over 40 years as an effective method for hearing rehabilitation in patients with conductive and mixed hearing loss who could not be rehabilitated with conventional hearing aids or surgery, as well as for single-sided sensorineural deafness (SSD) in more recent years. Traditional systems include an osseointegrated titanium implant with a percutaneous (skin-penetrating) abutment on which a bone conduction sound processor can be coupled. While the percutaneous system provides good results in terms of hearing and clinical outcomes as well as patient satisfaction, it still has some disadvantages due to the percutaneous coupling. Potential complications include loss of the titanium implant, recurrent soft tissue problems around the abutment (particularly when daily care poses problems), and potential aesthetic issues related to the percutaneous abutment [1], with some patients declining a percutaneous solution. In 1986, a transcutaneous (non skin-penetrating) bone conduction system, the Xomed Audiant, was introduced that had the potential to overcome these problems; however, disappointing output and skin complications resulted in withdrawal from the market [2-3]. Over the past few years, new transcutaneous bone conduction implants were introduced, including the Baha Attract System [4]. The Baha Attract System consists of a subcutaneous part, including a regular titanium implant on which an internal magnet is attached. Externally, a sound processor is attached to a second magnet and a soft pad, intended to distribute the pressure evenly over the underlying intact skin surface and thereby preventing pressure-related issues. Since initiation of the current study, several clinical studies have reported good results with this system, with favourable clinical outcomes and significant improvement in audiological outcomes compared to unaided conditions [5-12]. The current study was intended to add data on efficacy in terms of hearing performance and to evaluate safety of the Baha Attract System in a multicentre setting in the largest study on this new device to date. The present paper reports the results from the primary analysis after 6 months of follow-up. The patients will continue to be followed up for a total of 24 months.

Materials And Methods

Study design and participants

The aim of the current multicentre study was to compare the hearing performance of a transcutaneous bone conduction hearing implant system, the Baha Attract System (test device) manufactured by Cochlear Bone Anchored Solutions AB (Mölnlycke, Sweden), with unaided hearing and with the hearing performance of the same sound processor on a

Baha softband. Additionally, the study aimed to evaluate changes in subjective benefit and clinical outcomes with the test device compared to the preoperative situation.

Fifty-four adult patients with an indication for a bone conduction hearing implant were consecutively included in one of five participating centres starting May 2014: Queen Elizabeth Hospital Birmingham (Birmingham, UK), World Hearing Center Institute of Physiology and Pathology of Hearing (Warsaw, Poland), Manchester Royal Infirmary (Manchester, UK), Medical College of Wisconsin (Milwaukee, USA), and Radboud University Medical Center Nijmegen (Nijmegen, the Netherlands). Eligibility criteria for participation in the study are shown in Figure 1.

Adult subject, i.e. ≥ 18 years of age
Conductive or mixed hearing loss: bone conduction thresholds with a pure tone average PTA4* of <30 dB hearing level in the ear to be implanted OR Single-sided sensorineural deafness (SSD): bone conduction thresholds with a PTA4* of ≤ 30 dB hearing level in the good ear**
No previous bone conduction implant on the side of the skull to be implanted
Patients that are scheduled for unilateral implant surgery
At least 3mm soft tissue thickness at the planned implant site
Condition that could jeopardize osseointegration and/or wound healing should not be present (e.g. osteoporosis, psoriasis, use of corticosteroids, uncontrolled diabetes, radiation therapy at the same side of the skull as the planned implant)
Able to follow investigational procedures (e.g. to complete quality of life scales)

*mean of 500, 1000, 2000, 4000 Hz

** for US ≤ 20 dB hearing level AC in the good ear or indication for an AC CROS but cannot or will not use an AC CROS

Figure 1. Eligibility criteria

Surgery and follow-up

During the preoperative visit baseline characteristics were collected, and audiological and subjective hearing assessments were performed. During this visit a suitable sound processor was selected by the audiologist and the patient. Audiological outcomes, as exemplified below, were determined in an unaided condition and with the selected sound processor on a softband. All patients underwent a home trial of approximately one week (small variations depending on local clinical practice) with the sound processor on softband before consent for surgery.

A single-stage surgical procedure with placement of a 4mm BI300 Implant and a BIM400 Implant Magnet was applied in all centres (Figure 2a). The surgical technique involves an anterior based C-shaped flap 15 mm away from the edge of the implanted magnet (Figure 2b). Soft tissue thinning was advocated in case of >6 mm soft tissue thickness measured preoperatively and confirmed with a soft tissue gauge during surgery. Bone polishing was advocated in case of an uneven bone surface underneath the implant magnet. During implantation the Implant Stability Quotient (ISQ) was measured using resonance frequency analysis (RFA) at the implant level with the Osstell ISQ instrument and SmartPeg type 30

Figure 2a. Baha® Attract System

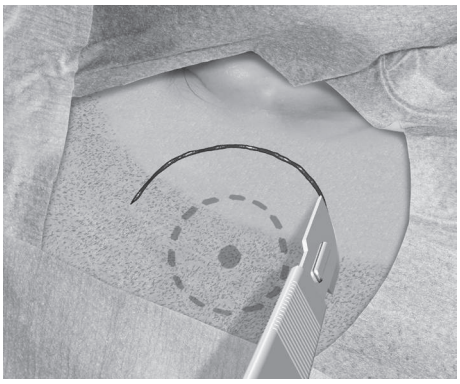


Figure 2b. Surgical incision, in two of the centres an anterior based flap was used

(Osstell, Göteborg, Sweden). The ISQ score ranges from 1 to 100, with increasing scores suggesting a more rigid implant-bone interface. Perpendicular measurements resulted in an ISQ low and ISQ high value [13]. Surgery time was measured as the time from first incision until last suture.

Follow-up visits were scheduled at 10 days (±5 days; wound inspection and removal of sutures), 4 weeks (±1 week; sound processor fitting), 6 weeks (±1 week), 12 weeks (±2 weeks), and 6 months (±4 weeks). During all follow-up visits the selected sound processor, the selected sound processor magnet (SPM) and the sound processor settings were evaluated. The sound processors that were available for use in the investigation were the Cochlear Baha 4 and BP110 sound processors. During the study, the Baha 5 Sound Processor became available and was used in two cases. The SPM is available in six different strengths, with SPM1 being the weakest and SPM6 the strongest. The sound processor magnet is selected based on subjective evaluation of the SPM retention and patient preferences. In case of an SPM change or when patient reported suboptimal fitting, re-fitting of the sound processor settings was performed, using BC Direct and feedback measurements (part of the fitting software).

Outcome measures

Primary outcome

Free-field threshold audiometry with the Baha Attract versus unaided preoperative assessment was chosen as primary outcome measure. From individual thresholds, the pure-tone average (PTA4, mean of 500, 1000, 2000, and 4000Hz) was calculated. Narrow-band noise was presented through a speaker in front position (0 degrees azimuth) according to the ascending or modified Hughson-Westlake method [14]. During the tests, the sound processor was set to omnidirectional mode and the non-test ear was blocked with an ear plug, in 2 centres additionally an ear muff was applied (Nijmegen, Kajetany).

Secondary outcomes

Secondary outcomes included free-field thresholds at individual frequencies (250, 500, 1000, 2000, 3000, 4000, and 6000Hz), speech perception in quiet and in noise. Speech in quiet was tested with monosyllables presented from the front (0 degrees azimuth). The percentage correct words at each presentation level (50, 65 and 80dB SPL) was recorded. Speech perception in noise was evaluated with sentences from the front (0 degrees azimuth) and with noise from the back (180 degrees azimuth). Noise was presented at a fixed level of 65 dB SPL while the speech level was adapted in 2dB steps to establish the level of 50% correct responses (SRT). The difference between the SRT and the noise level is the speech-to-noise ratio (SNR). During both tests, the sound processor was set to omnidirectional mode and the non-test ear was blocked. Due to differences in native languages, different speech materials and tests were used at the test sites (Birmingham and Manchester: QuickSIN test [15] and AB word lists [16]; Warsaw: Matrix test [17] and monosyllabic word test according to Pruszewicz [18]; Milwaukee: HINT [19] and CNC lists [20]; Nijmegen: Plomp&Mimpen [21] and NVA-Bosmanlijsten [22]). Absolute SNR scores were related to reference values for normal hearing patients for each specific test (Milwaukee -2.92dB [19], Nijmegen -5.4dB [21], Kajetany -9.6dB [17]) to enable comparison of data across sites; for evaluation of within-patient change in SNR the reference value is not required.

Clinical parameters comprised daily use of the sound processor in hours, number of episodes of insufficient retention per week, number of changes of the soft pad per week, and implant loss/removal. Pain was measured using a 4-point Likert scale; from no pain/discomfort to excessive pain/discomfort. Numbness was tested at randomly picked locations around the implant area with a pin and a cotton swab and was indicated as no numbness, numbness within 2 cm of the centre of the magnet or numbness (within and) beyond 2 cm of the centre of the magnet. Additionally, soft tissue status was scored as signs of infection, inflammation, skin necrosis or scar hypertrophy. Furthermore, any adverse events or device deficiencies were reported.

Magnetic retention force (MRF) was measured using a dynamometer (Baha Attract Force Gauge, Cochlear Bone Anchored Solutions AB), which measures the force in Newton (N) required to remove the external magnet from the skin overlying the internal magnet. The SPM soft pads used in the study showed a slight variation in thickness, resulting in approximately 0.1 Newton variability in MRF measurements.

Subjective benefit was measured by the Health Utilities Index (HUI3) [23], Abbreviated Profile of Hearing Aid Benefit (APHAB) [24], and Speech, Spatial and Qualities of Hearing Scale (SSQ) [25] questionnaires. The HUI3 is a generic preference based measure composed of 15 individual questions on 8 health-related quality of life dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each dimension is scored according to the utility approach from 0.00 for the lowest (highest degree of impairment or

disability) to 1.00 for the highest level (no impairment). Additionally, from these separate dimensions a comprehensive health state attribute is calculated.

The APHAB is a 24-item inventory, which is scored in four subscales on communication abilities or perception of sound in daily life situations (ease of communication, reverberation, background noise, aversiveness) and a global score. All items are scored on a 7-point scale indicating frequency of problems experienced, ranging from 1 to 99%, with higher scores indicating more problems.

The SSQ is composed of 49 items that are scored on a visual analogue scale with 0 representing complete inability and 10 representing complete ability or complete presence of a quality (or absence of need for effort). The questionnaire measures auditory disability across three subscales: hearing speech in a variety of contexts; directional, distance and movement components of spatial hearing and the ability to segregate sounds; and qualities of hearing including ease of listening, naturalness, clarity and identifiability of different sounds. For all subscales a mean score is calculated.

Sample size and statistical analysis

Sample size calculations were conducted to include enough power to detect a change on the primary outcome measure, PTA4 for unaided hearing versus hearing with the Baha Attract, as well as on the secondary outcome measure PTA4 softband versus Baha Attract. The power was set to 90% with a two-sided test with a significance level of 0.05. A within subject standard deviation of 3dB was assumed based on a previous internal study performed by the study sponsor. To compensate for a 10% dropout rate, a minimum of 52 patients needed to be included to detect a change of 1.5dB in free-field hearing thresholds on the secondary outcome measure. Sample size calculation was based on the full study population; due to the essentially different applications in conductive/mixed hearing loss (n=39) and SSD (n=15), results were analysed per type of indication. However, total group results are presented for the parameters that were used for the power calculation. Statistical analyses were performed by paired non-parametric tests based on non-normality assumptions. Paired measurements of audiometry and questionnaires were analysed using Fisher's non-parametric permutation test in an intention to treat analysis (ITT) (which included all patients that underwent surgery). Additionally, a per protocol population (PP) was defined which excluded patients with hearing tests performed significantly outside a visit window or not performed during the selected visit, and patients who did not have a refitting after a magnet change. All tests were two-tailed with significance levels of 0.05. Missing values were not imputed and no adjustments were made for multiple testing.

Monitoring at the European sites was performed by external monitors (Factory-CRO, Bilthoven, The Netherlands); monitoring at the US site was performed by monitors at Cochlear Americas (Denver, CO, USA). Data management was performed by external data managers (Factory CRO, Bilthoven, The Netherlands), and statistical analysis was realized

by external biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden) according to a predefined statistical analysis plan and using SASâ v9.4 (Cary, NC, USA).

Ethical considerations

The study was approved by all local ethics committees/institutional review boards and registered with ClinicalTrials.gov and assigned the identifier NCT02022085.

RESULTS

Patients and surgery characteristics

Results are presented for the intention to treat (ITT) population (n=54, all patients who underwent surgery). Similar outcomes were recorded for the per protocol (PP) population (n=49).

Sixty-one patients were screened for participation in the study, 7 patients were withdrawn from the study before surgery. Reasons for discontinuation before surgery were either eligibility failure (n=2) or withdrawal of consent (n=5). Three of the patients that withdrew consent opted for a percutaneous bone conduction hearing implant. Fifty-four patients were included in the study and underwent surgery between May 2014 and July 2015. Per centre, 12 patients in Birmingham, 14 patients in Warsaw, 4 patients in Manchester, 1 patient in Milwaukee and 23 patients in Nijmegen were included. Baseline characteristics are shown in Table 1. Thirty-nine patients were eligible for a bone conduction hearing implant because of a conductive or mixed hearing loss (mean PTA4 BC Baha side 11.4dB HL, SD 6.0, range 2.5-28.8), and 15 patients because of SSD (mean PTA4 BC good ear 8.1dB HL, SD 7.4, range -2.5-23.8 , mean PTA4 AC good ear 11.8dB HL, SD 10.4, range 1.3-42.5) (Figure 3). Mean surgery time was 38.7 minutes (SD 10.7; range 17-68 minutes). Soft tissue thinning was performed in 22.2% (n=12) and bone polishing was necessary in 20.4% (n=11) of the patients. ISQ measurements at implant level resulted in ISQ low 73.5 (SD 9.4; range 41.0-85.0) and ISQ high 77.3 (SD 9.0; range 41.0-90.0).

One patient discontinued the study after surgery; explantation of the implant magnet was required because of infection at the implant site appearing shortly after implantation. All other patients completed 6 months of follow-up.

Audiology

Free-field thresholds

On the primary outcome parameter, average free-field hearing threshold PTA4 with the non-test ear blocked, a significant improvement with the Baha Attract was observed compared to preoperative unaided hearing was observed at 6 months for the group of patients with conductive/mixed hearing loss (mean PTA4 difference -20.8dB, SD 9.8; *p<0.0001)*

Table 1. Baseline characteristics

Characteristics		Study group n=54
Gender	**Male**	21 (38.9%)
	Female	33 (61.1%)
Age at baseline	**Years**	42.1 (SD 13.6; range 18.3-70.3)
Smoking at baseline	**Yes**	14 (25.9%)
	No	40 (74.1%)
Indication	**Conductive/mixed**	39 (72.2%)
	SSD	15 (27.8%)
Bone conduction PTA*, mean (SD) dB	**Baha side (conductive/mixed)**	11.4 (SD 6.0)
	Good ear (SSD)	8.1 (SD 7.4)
Currently using a hearing aid	**Yes**	7 (13.0%)
	No	47 (87.0%)
Sound processor	**BP100**	1 (1.9%)
	BP110	23 (42.6%)
	Baha 4	28 (51.9%)
	Baha 5	2 (3.7%)
Study site	**Birmingham**	12 (22.2%)
	Warsaw	14 (25.9%)
	Manchester	4 (7.4%)
	Milwaukee	1 (1.9%)
	Nijmegen	23 (42.6%)

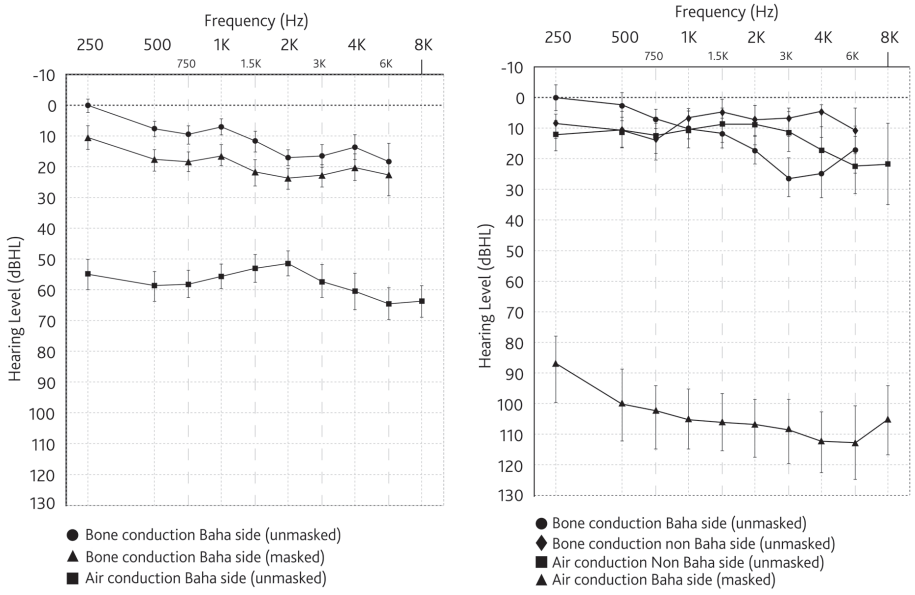
* 500, 1000, 2000, 4000 Hz

(Table 2a). For all individual frequencies, this significant improvement was observed (Figure 4a). Audiological results were similar at fitting as seen at 6 months follow-up.

Results with the test device at 6 months, were not statistically significantly different from the results with the same processor on a softband for the group of patients with conductive/mixed hearing loss (mean PTA4 difference – 0.3dB, SD 5.2; *p=0.73)*. When comparing individual frequencies, the results for the test device were statistically significantly better at 500Hz (mean difference -3.97dB, SD 7.6; *p=0.0026*) while more favourable results were obtained with the softband at 3kHz, 4kHz and 6kHz (mean difference at 3kHz: 3.46, SD 10.2, *p=0.027*; at 4kHz: 3.85dB, SD 9.1, *p=0.012*; at 6kHz: 6.0dB, SD 10.0, *p=0.0007*).

For the subgroup of patients with SSD, similar results were observed both compared to the unaided situation (mean PTA4 difference -21.6dB; SD 12.2, *p=<0.0001*) and compared to softband (mean PTA4 difference -1.5dB, SD 5.1, *p=0.27*).

Consequently, the total study population (presented for trial publishing obligations) showed similar outcomes compared to unaided hearing (mean PTA4 difference –21.0dB;



a. Conductive/mixed hearing loss **b.** Single-sided deafness

Figure 3. Audiogram preoperative (conductive hearing loss and SSD)

SD 10.4, *p=<0.0001*) and compared to softband (mean PTA4 difference –0.6dB; SD 5.1, *p=0.38*). Note that the non-test ear was blocked.

Speech in quiet and noise

Additional audiological measures in the conductive/mixed hearing loss group demonstrated statistically significant improvements in speech recognition in noise and in quiet for the Baha Attract as compared to the preoperative unaided condition (Table 2b). When comparing results of the (preoperative) softband application to the 6 months follow-up data with the test device, no differences were observed. There was a 5.0dB improvement in speech to noise ratio (SNR) compared to unaided and a 1.2dB improvement compared to softband. The difference in percentage correctly perceived words at 65dB in quiet was 44.5% more correct words compared to unaided and 3.0% less correct words compared to the device on softband. For the SSD group similar results were noted, however smaller differences in SNR were recorded compared to unaided (2.6dB improvement compared to unaided and 1.3dB less favourable compared to softband). The speech test in quiet at 65dB resulted in 40.7% more correct words compared to unaided and 0.2% more correct words compared to softband. The non-test ear was blocked in all the measurements.

In Table 2b absolute SNR values are presented adjusted to reference values for normal hearing listeners. It should be noted that by using reference values, negative values imply

that the results are worse than those of normal hearing listeners. Reference values were used in order to deal with different test characteristics. Nevertheless, even when reference values are being used, variability of test results between sites is not completely eliminated. SNR data from the site in Birmingham and Manchester were excluded from the analysis, due to invalid results for this specific test (incl. incorrect speaker set-up and presentation level of speech below patients' hearing thresholds). As a result the ITT population only for the SNR data included 27 patients in the conductive/mixed hearing loss group and 11 patients in the SSD group.

Clinical parameters

SP magnet selection and daily use

Choice of sound processor and sound processor magnets is presented in Table 2b. At first fitting, the most frequently selected magnets were the SPM5 or SPM6 (70%). During follow-up, a general decrease in magnet strength was noted, with SPM3 and SPM4 being most frequently selected at 6 months follow-up (57%). Sound processor magnets were adjusted according to patient preferences, including presence of pain/discomfort, insufficient retention, or clinical signs of increasing/decreasing soft tissue compression. As shown in Table 2b, many patients needed a magnet change at all follow-up visits, even at 6-months follow-up 75% of all patients required a decrease or increase in magnet strength. Mean magnetic retention force was stable over time, with a mean of 1.0-1.2 Newton at the different follow-up visits. However, the retention force varied between patients (range at 6 months visit: 0.3-2.2 Newton). In nine patients, the sound processor was replaced during the study period. Reasons for change of the initially selected sound processor mostly included availability of a newer sound processor and for one patient a change was needed because of magnetic retention difficulties (a smaller and lighter sound processor was selected). During the first weeks after initial fitting the sound processor was reported to fall off 4.5 times a week on average (SD 14.7); in the following weeks/months this number decreased to 1.8-1.9 per week. In the total group, average daily use was constant during follow-up, with a mean of 7.8 hours/day at 6 months (SD 4.6; range 0.5-18.0 hours/day).

Soft tissue problems and adverse events

During the study, four patients indicated excessive discomfort or pain at the implant site, which resolved spontaneously before final follow-up at 6 months. Some degree of discomfort/pain was stated by 60.4% of patients at 6 weeks; this number decreased to 37.7% of patients at 6 months (28.3% only slight discomfort/pain). No evident effect of soft tissue thinning on pain or numbness outcomes was observed. Numbness, reported by the patients during tests with either the pin, cotton swab or both, at the implant site was present for 64.2% of patients at the 6-week postoperative visit. At final follow-up this number

Table 2a. Audiology outcomes, intention-to-treat analysis

Outcome		Conductive/mixed hearing loss (n=39)					
		Pre-operative unaided (SD; range)	**Pre-operative softband (SD; range)**	**Fitting Test device (SD; range)**	**6 months Test device (SD; range)**	***Change pre-operative unaided to 6 months aided* (SD; range)**	***Change pre-operative aided to 6 months aided* (SD; range)**
Mean free field hearing tests: threshold audiometry PTA4*, dB		51.8 (SD 9.4; 36.3 to 54.9)	31.3 (SD 6.2; 16.3 to 43.8)	30.5 (SD 7.9; 18.8-55.0)	31.1 (SD 7.0; 18.8-52.5)	-20.8 (SD 9.8; -38.8-5.0) *p<0.0001*	-0.29 (SD 5.19; -10.0-13.75) *p=0.73*
Adaptive speech recognition in noise (50%, signal to noise ratio), dB**		9.3 (SD 7.1; 1.3 to 32.1) (n=25)	5.9 (SD 5.5; -1.4 to 19.6) (n=27)	5.4 (SD 4.6; -3.9 to 13.4) (n=27)	4.7 (SD 3.9; -1.8 to 11.4) (n=27)	-5.0 (SD 6.2; -23.9 to 5.1) *p<0.0001* (n=25)	-1.2 (SD 4.0; -8.2 to 6.8) *p =0.13 (n=27)*
Speech in quiet, % correctly perceived words	**50dB**	7.4 (SD 16.5; 0 to 60)	56.6 (SD 26.9; 20 to 100)	53.5 (SD 30.5; 0 to 100) (n=37)	61.2 (SD 22.8; 0 to 100)	53.8 (SD 27.6; -24 to 100) *p<0.0001*	4.67 (SD 27.3; -47 to 60) *p=0.29*
	65dB	44.4 (SD 32.4; 0 to 96)	91.8 (SD 9.2; 70 to 100)	89.6 (SD 12.4; 45 to 100) (n=37)	88.8 (SD 14.6; 30 to 100)	44.5 (SD 31.7; -3 to 100) *p<0.0001*	-3.0 (SD 11.7; -45 to 20) *p=0.12*
	80dB	82.4 (SD 23.5; 10 to 100)	96.9 (SD 5.7; 70 to 100)	96.6 (SD 4.9; 80 to 100) (n=37)	96.3 (SD 5.7; 70 to 100)	13.8 (SD 22.2; -20 to 80) *p<0.0001*	-0.67 (SD 4.7; -10 to 10) *p=0.4*

* 500, 1000, 2000, 4000 Hz

** adjusted to reference values for normal hearing Milwaukee -2.92 dB, Nijmegen -5.4 dB, Kajetany -9.6 dB

Table 2a. Audiology outcomes, intention-to-treat analysis

Outcome		SSD (n=15)					
		Pre-operative unaided (SD; range)	**Pre-operative softband (SD; range)**	**Fitting Test device (SD; range)**	**6 months Test device (SD; range)**	***Change pre-operative unaided to 6 months aided* (SD; range)**	***Change pre-operative aided to 6 months aided* (SD; range)**
Mean free field hearing tests: threshold audiometry PTA4*, dB		52.3 (SD 13.2; 23.8 to 81.3)	32.3 (SD 4.9; 21.3 to 38.8)	29.2 (SD 5.1; 17.5 to 36.3)	30.8 (SD 4.0; 23.8 to 37.5)	-21.6 (SD 12.2; -50.0 to 0.0) *p<0.0001*	-1.5 (SD 5.1; -11.3 to 5.0) *p<0.0001*
Adaptive speech recognition in noise (50%, signal to noise ratio), dB**		6.9 (SD 3.4; 0.3 to 11.8) (n=11)	2.99 (SD 3.1; -4.3 to 8.0) (n=11)	4.3 (SD 2.4; 1.0 to 7.7) (n=11)	4.3 (SD 3.4; -1.8 to 10.3) (n=11)	-2.57 (SD 3.9; -7.2 to 3.8) *p =0.051* (n=11)	1.3 (SD 4.2; -5.1 to 8.4) *p =0.34* (n=11)
Speech in quiet, % correctly perceived words	**50dB**	22.0 (SD 39.0; 0 to 100)	71.8 (SD 17.5; 48 to 100)	70.8 (SD 20.6; 30 to 100) (n=14)	69.5 (SD 17.9; 40 to 95)	47.5 (SD 33.6; -20 to 90) *p=0.0005*	-2.3 (SD 17.1; -50 to 27) *p=0.67*
	65dB	52.9 (SD 33.5; 0 to 100)	93.3 (SD 11.1; 60 to 100)	94.4 (SD 6.7; 78 to 100) (n=14)	93.5 (SD 6.1; 80 to 100)	40.7 (SD 31.8; 0 to 96) *p=0.0005*	0.2 (SD 7.1; -10 to 20) *p=0.94*
	80dB	85.2 (SD 15.0; 57 to 100)	96.7 (SD 5.4; 80 to 100)	97.8 (SD 3.0 ; 90 to 100) (n=14)	97.2 (SD 4.1; 90 to 100)	12.0 (SD 14.6; -10 to 43) *p=0.0059*	0.5 (SD 5.7; -10 to 10) *p=0.78*

* 500, 1000, 2000, 4000 Hz

** adjusted to reference values for normal hearing Milwaukee -2.92 dB, Nijmegen -5.4 dB, Kajetany -9.6 dB

Table 2b. Clinical outcomes, intention-to-treat analysis

Outcome		10D - Suture removal (n=54)	4W – Fitting (n=54)	6W (n=53)	12W (n=53)	6M (n=53)
SP Magnet	**SPM1**	-	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
	SPM2	-	1 (1.9%)	2 (3.8%)	9 (17.0%)	9 (17.0%)
	SPM3	-	6 (11.1%)	13 (24.5%)	15 (28.3%)	18 (34.0%)
	SPM4	-	9 (16.7%)	16 (30.2%)	11 (20.8%)	12 (22.6%)
	SPM5	-	19 (35.2%)	10 (18.9%)	12 (22.6%)	9 (17.0%)
	SPM6	-	19 (35.2%)	11 (20.8%)	6 11.3%)	5 (9.4%)
Magnetic retention force, Newton		-	1.0 (SD 0.4; range 0.3-1.7)	1.1 (SD 0.3; range 0.4-1.8)	1.2 (SD 0.4; range 0.3-1.9)	1.2 (SD 0.4; range 0.3-2.2)
Change of magnet	**No**	-	-	23(43,4%)	14(26.4%)	13(24.5%)
	Decrease	-	-	27(50.9%)	36(67.9%)	39(73.6%)
	Increase	-	-	3(5.7%)	3(5.7%)	1(1.9%)
Change of sound processor	**No**	-	49(90.7%)	51(96.2%)	52(98.1)	51(96.2%)
	Yes	-	5(9.3%)	2(3.8%)	1(1.9%)	2(3.8)
Daily use average, hours/ day		-	-	7.2 (SD 4.1; range 0-18)	8.3 (SD 4.7; range 1-18)	7.8 (SD 4.6; range 0.5-18)
Number of times sound processor fell off last week		-	-	4.5 (SD 14.7; range 0-80)	1.8 (SD 5.2; range 0-30)	1.9 (SD 7.1; range 0-50)
Number of soft pad changes per week		-	-	0.2 (SD 0.4; range 0.0-2.0)	0.2 (SD 0.2; range 0.0-0.9)	0.2 (SD 0.2; range 0.0-0.5)
Pain/discomfort	**No discomfort/pain**	-	-	21 (39.6%)	24 (45.3%)	33 (62.3%)
	Slight discomfort/ pain	-	-	15 (28.3%)	16 (30.2%)	15 (28.3%)
	Discomfort/pain	-	-	15 (28.3%)	11 (20.8%)	5 (9.4%)

Table 2b. Clinical outcomes, intention-to-treat analysis (continued)

Outcome		10D - Suture removal (n=54)	4W – Fitting (n=54)	6W (n=53)	12W (n=53)	6M (n=53)
	Excessive discomfort/pain	-	-	2 (3.8%)	2 (3.8%)	0 (0.0%)
Numbness with pin	**No numbness**	12 (22.2%)	15 (27.8%)	21 (39.6%)	33 (62.3%)	42 (80.8%)
	Numbness within 2cm	9 (16.7%)	7 (13.0%)	3 (5.7%)	5 (9.4%)	3 (5.8%)
	Numbness within/ beyond 2cm	33 (61.1%)	32 (59.3%)	29 (54.7%)	15 (28.3%)	7 (13.5%)
Numbness with cotton swab	**No numbness**	13 (24.1%)	18 (33.3%)	23 (43.4%)	31 (58.5%)	43 (82.7%)
	Numbness within 2cm	9 (16.7%)	6 (11.1%)	2 (3.8%)	6 (11.3%)	2 (3.8%)
	Numbness within/ beyond 2cm	32 (59.3%)	30 (55.6%)	28 (52.8%)	16 (30.2%)	7 (13.5%)
Problems soft tissue status*	**No**	54 (100%)	52 (96.3%)	51 (96.2%)	49 (92.5%)	51 (96.2%)
	Yes	0 (0%)	2 (3.7%)	2 (3.8%)	4 (7.5%)	2 (3.8%)

* were there any signs of infection, inflammation, skin necrosis and/or scar hypertrophy?

Table 2c. Subjective benefit questionnaires, intention-to-treat analysis

Outcome		Conductive/mixed hearing loss (n=39)			SSD group (n=15)		
		Preoperative (SD; range)	**6 months (SD; range)**	**Change**	**Preoperative (SD; range)**	**6 months (SD; range)**	**Change**
HUI	**Vision**	0.97 (SD 0.03; r0.95 to 1.00)	0.97 (SD 0.03; 0.95 to 1.00)	*p=1.00*	0.97 (SD 0.03; 0.95 to 1.00)	0.97 (SD 0.07; 0.73 to 1.00) (n=14)	*p=1.00 (n=14)*
	Hearing	0.62 (SD 0.33; 0.00 to 1.00) (n=38)	0.77 (SD 0.12; 0.32 to 1.00) (n=37)	*p=0.02 (n=36)*	0.73 (SD 0.33; 0.00 to 1.00)	0.76 (SD 0.07; 0.32 to 1.00) (n=13)	*p=0.68* (n=13)
	Speech	0.93 (SD 0.14; 0.41 to 1.00) (n=38)	0.98 (SD 0.06; 0.82 to 1.00)	*p=0.04 (n=38)*	0.94 (SD 0.17; 0.41 to 1.00)	0.98 (SD 0.09; 0.67 to 1.00) (n=14)	*p=0.75* (n=14)
	Ambulation	0.98 (SD 0.07; 0.67 to 1.00)	0.96 (SD 0.10; 0.67 to 1.00)	*p=0.25*	1.00 (SD 0.00; 1.00 to 1.00)	1.00 (SD 0.00; 1.00 to 1.00) (n=14)	*p= 1.00* (n=14)
	Dexterity	0.99 (SD 0.03; 0.88 to 1.00)	0.98 (SD 0.09 ; 0.45 to 1.00)	*p=1.00*	1.00 (SD 0.00; 1.00 to 1.00)	0.95 (SD 0.15; 0.45 to 1.00) (n=14)	*p=0.50 (n=14)*
	Emotion	0.93 (SD 0.12; 0.33 to 1.00)	0.95 (SD 0.13; 0.33 to 1.00)	*p=0.55*	0.89 (SD 0.18; 0.33 to 1.00)	0.91 (SD 0.18; 0.33 to 1.00) *(n=14)*	*p=0.70 (n=14)*
	Cognition	0.99 (SD 0.05; 0.70 to 1.00)	0.98 (SD 0.07; 0.70 to 1.00) (n=38)	*p=0.47 (n=38)*	0.87 (SD 0.23; 0.32 to 1.00)	0.91 (SD 0.19; 0.32 to 1.00) *(n=14)*	*p=0.50 (n=14)*
	Pain	0.91 (SD 0.14; 0.48 to 1.00)	0.92 (SD 0.13; 0.48 to 1.00)	*p=0.65*	0.89 (SD 0.11; 0.77 to 1.00)	0.93 (SD 0.08; 0.77 to 1.00) *(n=14)*	*p=0.18 (n=14)*
	Comprehensive health state	0.67 (SD 0.21; 0.32 to 1.00) (n=37)	0.74 (SD 0.199; 0.28 to 0.97) (n=36)	*p=0.11 (n=34)*	0.65 (SD 0.32; -0.14 to 0.97)	0.70 (SD 0.29; -0.06 to 0.93) (n=13)	*p=0.49 (n=13)*

Table 2c. Subjective benefit questionnaires, intention-to-treat analysis (continued)

Outcome		Conductive/mixed hearing loss (n=39)			SSD group (n=15)		
		Preoperative (SD; range)	**6 months (SD; range)**	**Change**	**Preoperative (SD; range)**	**6 months (SD; range)**	**Change**
APHAB	**Ease of communication**	41.9 (SD 24.3; 2.8 to 99.0)	16.9 (SD 14.9; 1.0 to 66.7)	*p<0.0001*	27.8 (SD 16.2; 10.5 to 76.5)	20.5 (SD 19.8; 1.0 to 64.2) (n=14)	*P=0.09* (n=14)
	Background noise	56.7 (SD 20.2; 18.8 to 99.0)	28.3 (SD 16.8; 8.3 to 68.5)	*p<0.0001*	68.2 (SD 15.3; 45.7 to 93.0)	48.6 (SD 22.0; 14.7 to 87.0) (n=14)	*P=0.0006* (n=14)
	Reverberation	52.1 (SD 18.7; 12.3 to 99.0)	25.9 (SD 14.6; 2.8 to 62.5)	*p<0.0001*	49.7 (SD 19.4; 24.7 to 97.0)	39.5 (SD 24.6; 2.8 to 93.0) (n=14)	*P=0.03* (n=14)
	Aversiveness	31.6 (SD 20.9; 1.0 to 76.7)	32.9 (SD 19.0; 1.0 to 74.5)	*p=0.71*	37.4 (SD 24.6; 2.8 to 93.0)	29.2 (SD 24.1; 1.0 to 68.3) (n=14)	*p=0.25* (n=14)
	Global	50.2 (SD 18.1; 15.2 to 99.0)	23.7 (SD 13.2; 5.3 to 59.7)	*p<0.0001*	48.6 (SD 13.5; 28.2 to 88.8)	36.2 (SD 17.1; 10.9 to 74.6) (n=14)	*P=0.0008* (n=14)
SSQ	**Speech**	4.4 (SD 1.5; 0.8 to 7.2)	7.1 (SD 1.4; 4.5 to 9.4)	*p<0.0001*	3.96 (SD 1.2; 1.8 to 5.6)	5.95 (SD 1.7; 2.7 to 8.5) (n=14)	*p<0.0001 (n=14)*
	Spatial	4.3 (SD 1.8; 0.7 to 8.3)	6.4 (SD 1.6; 2.2 to 9.2)	*p<0.0001*	2.7 (SD 1.3; 0.9 to 4.6)	3.9 (SD 1.8; 1.3 to 6.3) (n=13)	*p=0.04 (n=13)*
	Qualities	5.8 (SD 1.4; 2.6 to 8.7)	7.6 (SD 1.4; 4.3 to 9.7)	*p<0.0001*	5.7 (SD 1.3; 3.0 to 7.97)	7.2 (SD 1.3; 4.7 to 9.1) (n=14)	*P=0.0002 (n=14)*

decreased to 20.8%. Soft tissue problems recorded as a predefined standard evaluation at each visit, i.e. infection, inflammation, skin necrosis and/or scar hypertrophy, occurred with a prevalence of 3.7, 3.8, 7.5 and 3.8% at fitting, week 6, week 12 and month 6, respectively. These included one patient with minor skin pressure problems/necrosis, all other events were minor soft tissue infections or inflammations which resolved by local treatment.

A total of 43 patients presented with adverse events during the study of which 27 patients experienced 36 device related events, mostly recorded as pain/discomfort (n=25 events in 18 patients). Four reports in four patients were made of pressure related skin complications and one report was made of magnetic retention difficulty. One device related serious adverse event was reported; a patient with infection at the implant site that required surgical removal of the implant magnet shortly after implantation. The related adverse events were partially overlapping with the abovementioned predefined study parameters collected at each visit.

Questionnaires

In the HUI3 questionnaire most attributes were scored high during the preoperative measure and no further improvement was noted during the study. In the conductive/mixed hearing loss group, however, for the hearing attribute a statistically significant improvement was recorded (mean +0.14, $p=0.02$). Additionally, an improvement was observed for the speech attribute, albeit smaller and with a high initial score (mean +0.05, $p=0.04$). For the comprehensive health state a non-significant improvement was noted (mean +0.06, $p=0.11$) (Table 2c). In the SSD group, smaller and non-significant differences were observed (comprehensive health state mean +0.06, $p=0.49$).

The APHAB questionnaire showed significant improvement in terms of the global score in the conductive/mixed hearing loss group (mean global improvement 26.5%, $p<0.0001$). Furthermore, statistically significant improvements for all subscales except for the aversiveness score were recorded. In the SSD-subgroup less improvement on the global rating was noted (global mean improvement 12.9 %, $p=0.0008$).

The SSQ questionnaire showed improvements for all subscales in both subgroups of patients with conductive/mixed hearing loss and those with SSD, though not all improvements were statistically significant. The SSD patients showed slightly lower pre- and postoperative scores and less improvement compared to the conductive/mixed patients, with lowest scores and least improvement on the spatial domain (Table 2c).

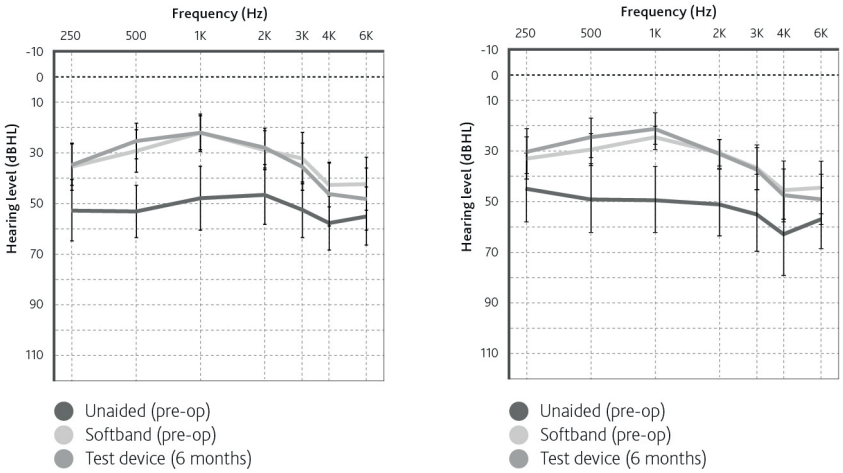


Figure 4a. Free-field threshold audiometry on individual frequencies

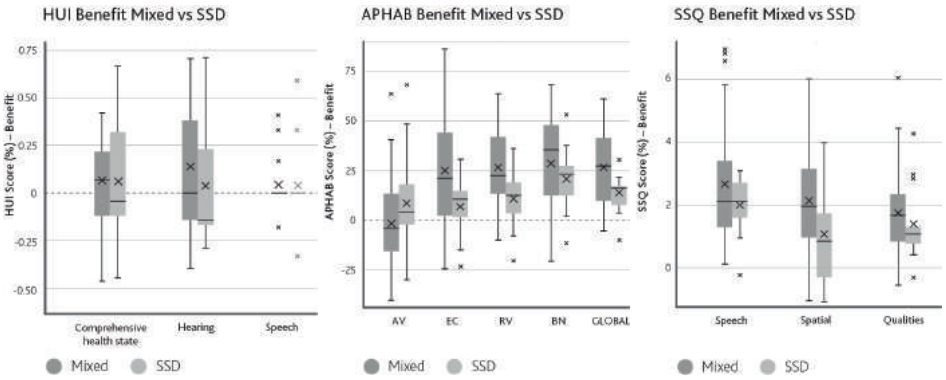


Figure 4b. Subjective benefit as measured by the HUI, APHAB and SSQ questionnaires.
Completed before surgery and after 6 months, change in scores is depicted for both indications. The mean (cross) and median (horizontal bar) are defined within each plot, boxes represent interquartile range, whiskers represent 95% range and dots represent outlier values.
AV = aversiveness, EC = ease of communication , RV = reverberation, BN = background noise

Discussion

Key findings

The results of the present investigation showed in general favourable audiological outcomes and subjective benefit on the questionnaires with the Baha Attract compared to unaided conditions. For patients with conductive or mixed hearing loss significant improvements were observed in free-field hearing thresholds and speech perception in quiet and noise

compared to unaided hearing. For patients with SSD, significant improvements were observed in free-field hearing thresholds and speech understanding in quiet and non-significant improvement for speech understanding in noise. However, compared to the preoperative measurement with softband, no differences were found in free-field hearing thresholds, speech in quiet and speech in noise in both groups. All audiology tests, including the unaided test, were executed with the non-test ear blocked. The most important soft tissue problems observed during follow-up included numbness, pain/discomfort at the implant site and to a lesser extent pressure related skin complications. A declining trend was noted in the rate of these complications at 3-6 months.

Strengths and limitations

The current study presents the largest multicentre prospective data on the Baha Attract System to date. Evidence is provided on all aspects of outcome measures relevant for device evaluation. Hearing related outcomes and clinical parameters, as well as questionnaire data is provided according to a predefined study protocol. A consideration in the selected design might be the within-patient control. Choosing a within subject design reduces the amount of error arising from natural variance, which is especially important in outcomes with a high variance like hearing thresholds, hence the choice of the design. The comparison to unaided hearing could provide a good measure of experienced benefit achieved with the Baha Attract. However, a comparison with the current gold standard, the percutaneous solution, would make a stronger case for the test device. Thus far, no prospective studies have been reported with a percutaneous control, only a single retrospective case series [8]. All other reports use the same within-patient design or compare the Baha Attract with other transcutaneous devices and generally show adequate results on clinical and audiological outcomes [5-7,9-11,26]. For patients with SSD, some studies, showed slightly less favourable audiology data and higher non-usage [12,26].

Other consideration deals with the study design. Looking back, the predefined pooling of the data of both indications (conductive/mixed hearing loss and SSD), was not optimal. Therefore, the choice was made to present the data separately. Furthermore, to fully assess the benefit of the Baha Attract in SSD patients, a distinct set-up for the speech in noise test, with noise presented from the side instead of the back, might have been preferred. Additionally, the choice to block the non-test ear during the audiology tests is likely to have resulted in an overestimation of the effect of the test device compared to the normal unblocked situation, especially in SSD patients. At last, for the speech in noise tests the fixed noise level of 65dB SPL might not have been audible to all patients in the preoperative unaided situation. Therefore, regarding the speech in noise performance the comparison with the softband is more informative.

Last but not least, the current results are from the mid-term evaluation; the long-term outcomes have to be awaited and will be presented after 24 months of follow-up.

Interpretation

All previously published studies report good results on soft tissue status post implantation with the test device, with few problems regarding pain at the implant site (most of which resolved with a reduction of magnet strength) and resolving numbness scores during follow-up. The only study reporting relatively high prevalence of numbness is a small case series by Carr et al., where eight out of ten patients reported presence of numbness at some point during follow-up [10]. Furthermore, Dimitriadis et al. reported mostly minor skin issues (redness and tenderness) in pediatric patients implanted with the Baha Attract, while two patients presented with a skin dehiscence over the magnet [27]. Skin necrosis is reported by two other case reports, and it was suggested that a strict post-fitting monitoring is critical in avoiding these complications [28,29]. Since the results of the current study, showing approximately 20% of patients with any degree of numbness and 38% with (slight) pain/discomfort at 6 months of follow-up, deviate slightly from the other available evidence with better results on these clinical outcomes, it should be concluded that further and long-term research on these issues is needed. Numbness is also observed with the use of traditional percutaneous bone conduction hearing implants placed using soft tissue reduction surgery, yet few clinical investigations have evaluated and reported on numbness in a systematic way. Despite it being difficult to compare these numbers to available studies on percutaneous implants, from a clinical perspective it would be desirable to improve these numbers. A possibility to accomplish this reduction might be to modify the surgical incision and minimize trauma to nerves and vessels, e.g. by using a less invasive, shorter and more superior curved or linear incision [30]. The clinical outcomes after 24 months of follow-up of the patients in this clinical investigation will be of particular interest, in order to understand if the continuous improvement in numbness and discomfort/pain seen during the first 6 months continues over the longer term. The ISQ measurements at surgery varied widely, though no osseointegration problems were noticed. The measurements in the current study were done at implant level, consequently the numbers are not comparable to previous reports at abutment level in literature [13]; these measurements have their own merits, amongst others in creating reference values.

Results on hearing amplification are comparable to previous reports with outcomes comparable to those with a sound processor on softband or other transcutaneous devices. Compared to percutaneous bone conduction implants, transcutaneous systems provide less efficient sound transmission (especially at high frequencies) due to dampening by the intervening soft tissue layer. Early reports have shown that application of a passive transcutaneous device via a headband or testband result in dampening of 15-20dB for the frequency range from 1 to 4kHz [31,32]. More recent studies indicate similar slightly inferior hearing thresholds with the use of a magnetic transcutaneous system as compared to a percutaneous abutment [33]. With respect to different frequencies, a less favourable result of the Baha Attract was noticed in the high frequencies, which are especially important

for speech understanding. While transcutaneous systems suffer from less efficient sound transmission compared to percutaneous devices, they obviously have some important other advantages. These advantages include no need for daily care of the skin around the skin penetrating abutment, less risk of implant loss and infection, and potentially improved cosmetics, which might explain the recent increased interest for transcutaneous options. For patients that require a powerful solution, e.g. due to a significant (high-frequency) sensorineural component in their hearing loss, percutaneous devices remain the gold standard. In patients with SSD, free-field hearing thresholds with the Baha Attract that were equal or worse compared to the expected attenuation by the head-shadow effect were recorded in the majority of patients (aided thresholds >10-20dB poorer than the preoperatively measured AC thresholds in the good ear). This suggests that, to ensure good outcomes in this population, the patient should have normal or near-normal hearing in the good ear. While the sample size in the SSD group was too small to draw statistically supported conclusions, our clinical experience and the individual data of the SSD patients supports this recommendation. An important aspect to include in the candidacy selection for bone conduction implants is longevity, i.e. taking into account the deterioration of sensorineural hearing loss owing to ageing or progressive cochlear disease (www.snikimplants.nl). With the Baha Attract, the option remains to change to a percutaneous solution as the implanted magnet is attached to the same titanium implant as the abutment in percutaneous application. More recently, more powerful sound processors have become available, enabling potentially more patients to benefit from transcutaneous systems in the future.

Generalizability

The results of the current multicentre prospective study adds important data on a still relatively new and infrequently studied magnetic transcutaneous implant system. Since hearing results were generally comparable to a condition with a sound processor on a softband, a preoperative trial seems of vital importance in a clinical context for preoperative evaluation of patients. When discussing different bone conduction options, the slightly more invasive surgery and less favourable MRI-compatibility compared to percutaneous devices should be taken into consideration. Furthermore, audiological indications still have to be determined. Up to now, restrictions to bone conduction thresholds better then 30-35dB HL or even more conservative limits have been mentioned in the literature [4,34], however, the recent availability of more powerful sound processors might affect this restriction.

Further research is warranted, including an appraisal of all available options. This accounts to the audiology criteria but also clinical parameters like soft tissue problems. A direct and objective comparison on numbness and pain/discomfort problems, but also on other issues more likely for percutaneous implants like peri-implant disease and implant loss, for all different available systems are not available in the literature to date. Recent suggestions on a new scale to evaluate the skin at the implant site usable for both percutaneous

and transcutaneous systems might make it possible to obtain a good comparison between systems [35].

Conclusions

The present multicentre study showed that the Baha Attract System provides improvement in hearing performance and subjective benefit compared to the preoperative unaided condition (with the non-test ear blocked). Hearing performance of the Baha Attract was similar to that obtained with the same sound processor on a softband. Based on the results of the current study, the Baha Attract system could be considered as a treatment option for patients with conductive/mixed hearing loss with relatively favourable bone conduction thresholds. For patients with SSD a more careful selection procedure is suggested. A pre-operative softband trial provides the patients with a representative experience of the post-operative hearing outcomes and should be part of the decision making process before fitting a patient with the Baha Attract System. Since these clinical results are still mid-term and not stabilized at the end of follow-up, the results of 24 months have to be awaited to present more definitive conclusions. The current results, in combination with increasing options in bone conduction implants, emphasize the importance of a well-informed patient and shared decision-making.

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chapter 9

General discussion and summary

General discussion

Since the first implantation of a bone conduction hearing implant in 1977 [1], emphasis in research has been on the clinical evaluation of the system, in terms of implant stability, soft-tissue outcomes and audiological results, for different patient groups and various indications. In the past decade, the rapidly evolving availability of new designs in implant systems and subsequent new surgical techniques has had its influence on the scope of research [2]. In this chapter, evaluation of clinical and audiological outcomes, and the effectiveness of new implants and surgical techniques in bone implant research are further discussed.

Effectiveness and safety of implants in current practice

In Part 1 of this thesis several clinical outcomes were evaluated within various domains. Chapter 2 describes a large patient cohort, in which the association between several comorbidity risk factors and complications of bone conduction hearing implants was evaluated. The study included 581 adult patients with a total follow-up time of 7120 years, the longest follow-up on bone implant complications reported thus far. Implant loss was observed in 7.5% of implants and adverse soft tissue reactions in 18.4% of implants. Several factors could be identified as a risk factor for complications. Firstly, for soft tissue reactions, skin disease was the only statistically significant risk factor in both univariate and multivariable analysis. Female gender showed a trend to a negative risk factor. Secondly, concerning revision surgery, both smoking and female gender appeared to be independent negative risk factors. Thirdly, for implant loss, smoking could be identified as a risk factor. The possible pathophysiological mechanisms behind these associative factors are discussed in the manuscript and supportive evidence was reported [3-11]. Other previously reported risk factors like BMI [12-14] and diabetes mellitus [15] could not be confirmed in this study. Remarkably, the complication rate was relatively high compared to more recently reported complication rates [16,17]. The length of the follow-up might explain this higher rate. However, it was primarily assigned to the inclusion of previous generation implants and previous surgical procedures, which were more prone to complications (See Part II). This study could therefore serve as a historical control in future comparisons or a reference, since large cohort studies have previously proven their value as a reference within the field [10,18-21]. Additionally, it was suggested to include the identified risk factors in counselling patients. Up to date, no comparably large studies on comorbidity influences are available neither for new implants, nor for recently introduced surgical techniques.

In chapter 3 the clinical results of the Cochlear™ BI300® implant were retrospectively reviewed in 79 children, who were treated since the introduction of this new implant type in the Radboudumc Nijmegen and Birmingham Children's Hospital. This study was initiated

to gain more insight into an observed increase in soft-tissue complications in our paediatric patient population since the introduction of this new implant. The study confirmed good implant survival for the new implant type (96,5% survival during a mean follow-up 11.7 months), noticeably, this percentage is higher compared to what was reported for previous generation implants [10,12,22-24]. The number of adverse soft tissue reactions appeared to resemble numbers reported on previous generation implants in children. Relatively more soft tissue overgrowth was noted. The resultant was an increased number of revision surgeries since the introduction of the BI300; in 28.7% of implants one or multiple revision surgeries were required, much higher compared to what was reported earlier [22,24]. This increase in complications involves more visits to the outpatient clinic and (temporarily) non-use of the sound processor. An observed disparity in clinical results between the two participating centres (relatively more soft tissue problems in the Birmingham cohort), was attributed to differences in case mix, treatment protocols, data collection and documentation. The greatest limitation however, was the lack of a control population, precluding a direct comparison with the results of the previous generation implants and identification of possible confounding factors. Nevertheless, the study is of importance for its observation of less favourable clinical results in the paediatric population. As a result, treatment policy has changed considerably. At present longer abutments are implemented, since in previous studies it has been observed that longer abutments can reduce soft tissue problems [25]. These longer abutments either replace the shorter one as an outpatient clinic procedure in the children of the study (who are old enough to undergo an abutment change in outpatient clinic), or are used at primary implantation, combined with tissue preservation technique, for newly treated children. The study emphasizes the relevance of prospectively collected clinical data at introduction of any newly designed implant or implant system, not only in adults, but also (and maybe especially) in children and other more vulnerable patient populations who are generally excluded from the first clinical trials.

Aside from clinical outcomes, like implant survival and soft tissue outcomes, evaluation on audiology measures was included in the current thesis. In Chapter 4 directional hearing was studied in children with bilateral conductive hearing loss using bilateral bone conduction devices. Spatial discrimination, (whether sound is heard on the left or right side) was evaluated with the minimum audible angle test. True sound localization (the accuracy of processing binaural cues), was tested with a sound localization test [26]. By presenting the stimuli at randomly selected locations in a dark environment and by roving of the presentation level, we attempted to exclude previously described limitations and therefore being able to objectively study the binaural hearing with bilateral bone conduction devices [27-31]. Eleven children participated in the study. Ten out of these eleven participants were children with bilateral atresia, with accompanying congenital conductive hearing loss. Both tests were conducted in a condition with bilateral BCDs and in a unilateral left

and right condition, in randomized order. Bilateral application resulted in better spatial discrimination, as well as better sound localization. However, while spatial discrimination showed good results in nearly all children, the localization test showed that most children in this study demonstrated lateralization behaviour rather than actual sound localization, implicating that these children can distinguish sounds coming from the left or the right side, without being able to indicate the exact sound source location. Interesting differences were noticed between the children with congenital conductive hearing loss and the only child with acquired conductive hearing loss. In the bilateral BCD condition the child with acquired conductive hearing loss was able to localize sounds close to the ability of normal hearing subjects. Good localisation in patients with acquired conductive hearing loss was previously noticed in a study by Bosman et al [28] and could be matter of further research. It is suggested that early experience with binaural hearing might be essential for good sound localization. Despite the fact that the patients with bilateral congenital conductive hearing loss were not able to localize sounds accurately, they were able to lateralize sounds, which is important in daily life situations; for example in the determination the direction of sound in a classroom or outdoors. This potential benefit of bilateral fitting can be used in counselling patients and/or parents.

Optimizing patient indications for a bone conduction hearing implant is a valuable development. The currently developed Dutch national guideline, as well as other national guidelines, and consensus or quality standards for bone conduction implants, are expected to help selecting the right patients for bone conduction hearing implants, and providing optimal personalized healthcare by including guidelines for minimum diagnostic processes, surgery and audiological follow-up and organization of care [32-34]. Future studies on bone conduction device non-use might identify pre-operative predictive parameters to aid individualized (i.e. patient centered) care. Good patient selection is not only of importance for patients, but also in a societal perspective. Increasing costs of bone conduction hearing implants, including costs of sound processor replacements every five years, are a growing burden on hospital budgets in the Netherlands. Dedicated outpatient teams, in which medical specialist and audiological teams work together and are able to provide the full-set of rehabilitation and surgical options (or at least are able to advice on all options), remain of crucial importance in this respect [32]. Especially in low-volume patient care, like paediatric bone conduction implants or patients with craniofacial abnormalities, dedicated teams are important in diagnostic and therapeutic challenges. Chapters 3 and 4 highlight the importance of outcome evaluation in these groups. Chapter 3 additionally highlights the value of (inter)national collaboration and the value of uniform outcome evaluation and reporting. Another initiative that is expected to aid uniform outcome evaluation in the near future is Auronet. Auronet is an international group of dedicated professionals developing

a core set of patient-centered outcome measures to guide individual practice and act as a standard of reporting in clinical trials [35].

New implants and surgical techniques

In the second part of this thesis, the evolving availability of new implants and subsequent surgical techniques during the past decade is discussed. Before 2009 a single implant-abutment system was available; the flange fixture from Cochlear™. In 2009 the company Oticon Medical™ introduced the Ponto® system with a classic Ponto® implant-abutment, with a different design compared to the already available system from Cochlear™. The novel shoulder shaped abutment resulted in adequate soft tissue outcomes and the standard diameter implant showed good implant survival in the first reports [36]. At the same time a multicentre randomized controlled trial was initiated to study a new wider implant from Cochlear™. This new implant was designed with an altered surface technology (moderately rough TiOblast®) and a wider diameter implant. These alterations were intended to increase stability and reduce implant loss. The abutment was rounded and apically converging, intended to decrease adverse soft tissue reactions. This system became commercially available afterwards as the BI300® implant-abutment system. The results from a three-year randomized controlled trial were very promising (both at 6-months and 3-year follow-up), with a reduction in soft tissue reactions and higher ISQ (implant stability quotient) values [37,38]. These results were also noted in other studies on the same implant [39-43]. Subsequently, the previous generation implant was completely replaced by the BI300 over the next few years. However, given the importance of long-term follow-up (bone conduction hearing implants remain in situ during several decades), the results on outcome measures of the initial trial participants were once more assessed at a five-year follow-up visit. In addition, the incentive to perform a five year post-implantation assessment was supported by an average drop in ISQ value in the last year of the original trial [37]. In chapter 5 the results of this long term follow-up are described. The initial trial comprised 52 test implants and 25 control implants (all part of the implant survival analysis). The five-year follow-up visit included 40 test implants and 17 control implants. For both groups of implants, the ISQ values recovered from the previous drop and the mean ISQ values at 5 years were higher compared with values at implantation. However, no difference was noticed in ISQ increase from baseline between the two groups of implants. Implant survival was high in both groups (95% versus 95.8%). Furthermore, the results on soft tissue reactions were superior for the BI300 implant (2.5% versus 23.5%), confirming the positive results from the previous trial. It was concluded that the current results supported the replacement of the previous generation implant by the new BI300 implant for adult patients. The primary outcome parameter in the original trial, ISQ, has been has been subject to discussion in the past few years. Absolute ISQ values are difficult to interpret, due to previously reported heterogeneous data and the influence of implant and abutment type and length on absolute

values [44,45]. Furthermore, the relation of ISQ and implant loss has not been confirmed up to now, which questions the clinical importance that can be assigned to absolute ISQ-values in current practice. Several suggestions were done by Nelissen et al. for future research and clinical use of this outcome [44]. In the case of the BI300 system the positive soft tissue outcomes in adults have proven to be of clinical importance for these patients.

Since the initial randomized controlled trial on the BI300 versus the previous generation flange fixture, several initiatives for further improvement of implants and abutments have been undertaken. Most modifications are intended on increasing implant stability and reducing implant loss, like the Oticon™ wide implant (wider implant diameter). In chapter 6 the results of a randomized controlled trial on this Oticon™ wide implant are discussed. Fifty-seven patients with 60 implants were included in this trial with a randomization ratio of 2:1 (test versus control). The new wider test implant showed a significantly higher ISQ value (ISQ high and low) compared to the control implant. Additionally, the increase in average ISQ was significantly more for the test implant. No implants were lost in either group. Other clinical outcomes like adverse soft tissue reactions were comparable between the test and control implant. Based on these outcomes the previous generation 3.75 mm wide implant was replaced by the new, wider implant. This study was continued to 3 years and the complete study shows similar results at final follow-up [46].

Other modifications on the implants and abutments are all still in clinical or preclinical trial phase, with consequently limited data available. One of these newer modifications is the Cochlear™ BI400®, with a hydroxyapatite coated abutment to achieve a tight skin-implant connection, aiming to further reduce soft-tissue problems. The first case series on the BIA400 failed to show an evident positive effect on soft tissue outcomes [47,48], and results of a larger trial are awaited [49]. Another implant modification intended to increase implant stability and reduce implant loss, is the Oticon™ BHX. This implant has a laser modification of implant surface and hereby, hypothetically, an improved biomechanical anchorage. The first results on this implant have recently been published [50]. In this patient cohort of 34 participants, one implant loss was reported. The ISQ values were comparable to previous reports on the Oticon™ wide implant.

It could be questioned whether all the present, and possible alterations in design of the percutaneous implant in the future are beneficial, since the complication rate is already low in the currently used implants in the adult patient population. Incremental costs of new designs are only warranted if it leads to significantly better patient care. The currently available percutaneous bone anchored hearing implants have low complication rates and good clinical results. If there is little room for improvement, it could be doubted whether

new designs are a cost-effective, and resources should perhaps be attributed to other aspects of bone implant research.

Introduction of new medical devices and current regulation has been of interest in scientific and policy discussions over some time now [51-57]. Failures of metal-on-metal articulations in total hip replacements [58] and the PIP breast implant scandal [59,60], amongst others, have emphasized the need for more thorough and evidence based introduction of devices, and for timely evaluation.

Pharmaceutical approval processes pose considerably more methodological boundaries than those that apply for medical implants, where only evidence of safety needs to be shown before commercial availability [61,62]. Moreover, after these safety trials, commonly so-called post-market trials are initiated. These trials not only serve the evaluation of safety and effectiveness to aid clinician and patient in device selection, but are also deployed as a marketing tool (and to support medical claims) [63,64]. One may think that otological implants pose little risks to patients, a recall of highly magnetic stapes prosthesis in 1987 and a cochlear implant positioner causing an increased incidence of bacterial meningitis in 2002, however, suggest otherwise [65,66]. Therefore, approval should be based on prospective comparative effectiveness trials of high-quality and sufficient duration [51,54,67,68]. Ideally these trials should either not be industry sponsored or without interference of the manufacturing company in trial design, result analysis and reporting, given the widely available evidence of bias by industry sponsorship [69-72]. Furthermore, routine data is suggested to be used to monitor newly introduced implants, for example in national and international registries [64,73]. The scale of uncontrolled device introduction may not be fully recognized and consequences even less known [74]. In other medical specialities, the device failures have resulted in implementation of (inter)national device registries. In the field of otology initiatives for national registries are currently also explored [34].

The problem of late evaluation of new developments is not merely a problem in medical device introduction. New surgical techniques are developed and widely applied in clinical practice before thorough evaluation, as surgical innovation is not subjected to any formal regulation. Despite the lack of mandatory guidelines, the importance of timely evaluation of new techniques is recognized [55-57]. In chapter 7 a new surgical technique within bone implant research, a modification of the standard linear incision technique [75,76], is presented. For many years a soft tissue reduction step was applied during the implantation of a percutaneous implant. It was assumed that a thin, and immobile skin around the abutment reduced the chance for soft-tissue infections and improved the sound transmission. Hultcrantz et al. introduced a simplified surgery without skin reduction and reasonable short-term results were reported [77]. One of the grounds for this innovation was the recent availability of longer abutments, which is an important condition for the possibility of tissue

preservation, since previous 6mm abutments are generally not long enough to perforate the complete skin. The new tissue preservation technique was conducted in 25 patients in our centre, comparing them to 25 trial patients from a previous study with soft tissue reduction (discussed in chapter 6). Results on audiology outcomes were similar for both techniques and a significant shorter surgery time was recorded for the preservation technique. An increase in minor soft-tissue reactions after 6 months was observed (n=7 versus n=1, p=0.049). This increase in adverse soft-tissue reactions was not evident in the first study by Hultcrantz et al. or subsequent studies by the same or other authors [77-82]. Based on these conflicting results, the need for a more elaborate evaluation and long-term follow-up was stated. The results of the three-year follow-up are expected in the near future. Meanwhile the bone implant surgery techniques have been adjusted in several centres already, with a minimally invasive punch technique being one of the latest developments for implantation of percutaneous implants. In our view, published results of this technique are still sparse [49,83,84] and some restraint in adopting this technique seems appropriate. Especially since the punch technique involves less surgical exposition, which makes adequate visualisation and cooling less easy. Experience with implantation of bone conduction hearing implants in a standard technique seems advisable before using this technique. Given the good clinical results of the standard (linear) incision techniques, again, it could be questioned how much room for improvement there is with adjustments in the current surgical technique.

As already stated in the introduction, another development within the field is the revival of transcutaneous systems. These transcutaneous systems are introduced with the potential to overcome some of the remaining disadvantages of the percutaneous coupling. These include loss of the titanium implant, possible recurrent soft tissue problems around the abutment in specific patients (particularly when daily care poses problems), and potential aesthetic issues related to the percutaneous abutment. In chapter 8 the six-months results of a trial on the transcutaneous Cochlear™ Baha® Attract are presented. The multicentre trial included 5 centres and 54 patients, with either a conductive/mixed hearing loss or single-sided deafness (SSD). A significant proportion of the patients reported pain or numbness during the follow-up, especially during the first postoperative weeks. Most cases of pain resolved or reduced with changing the magnet to a less strong one, however, in several cases the device could (temporarily) not be worn as a result. Several patients presented with long term complaints of pain/discomfort (21% of patients at 6 months) and/or numbness (38% of patients at 6 months). No major soft tissue problems like soft tissue necrosis were noticed (which is reported in case reports, both after conversion from percutaneous to transcutaneous implants, and after initial transcutaneous fitting [85-87]. Good results on the subjective benefit questionnaires at 6-months were observed compared to the preoperative (unaided) situation. For the free-field hearing thresholds in both groups (SSD and conductive/mixed hearing loss) an improvement was observed compared to

unaided hearing, however, not compared to the preoperative measurement with softband. It should be noted that all the audiological tests were all conducted with the non-test ear blocked, resulting in an overestimation of the effect of the test device compared to the normal unblocked situation, especially in SSD patients. Improvements were also recorded in speech tests in quiet and noise compared to unaided hearing for the conductive/mixed hearing loss group and for speech in quiet in the SSD group. Again, no improvements were noticed compared to the softband condition in these outcomes. In these results the limitations regarding the blocking of the non-test ear apply as well. Furthermore, in the speech in noise tests the fixed noise level of 65dB SPL was probably not audible to all patients (in the preoperative situation). This resulted in an overestimation of the effect of the Baha® Attract compared to the 'unaided' condition. The comparison with the softband is deemed more informative. Since the softband provides a representative experience of the post-operative hearing outcomes with the Baha® Attract, it was advised that a pre-operative softband trial should be part of the decisionmaking process before fitting a patient with the Baha® Attract System. For single-sided deafness patients and those patients that require more amplification, e.g. due to a significant (high-frequency) sensorineural component in their hearing loss, a restrained recommendation was suggested for the Baha® Attract based on a clinical perspective and individual patient data (free field hearing thresholds with the Attract worse compared to the expected attenuation by the head-shadow in the individual data of the majority of patients). As previously stated the skin dampening of transcutaneous devices results in a significant threshold decline of 5-20dB for frequencies 1-4kHz compared to percutaneous solutions [88,89]. Important to take into account in this respect is the deterioration of sensorineural hearing loss owing to ageing or progressive cochlear disease, i.e. the longevity of the bone implant (www.snikimplants.nl). Despite several challenges in analysis and interpretation of the data (underpowered results due to inability to combine the results of different indications, and different audiology tests with set-up restraints), a result of unfortunate choices in the trial design, the results of the study are important in determining the selection criteria for these new implants and for patient counselling during the preoperative decisionmaking processes. The trial will continue to a follow-up of two years. These results and direct comparisons with the percutaneous bone implant and other available options are awaited. Several clinics reported in verbal communications that up to more than half of their patients are implanted with a Baha® Attract nowadays. This market share of the Baha® Attract is remarkable in the light of its' appearance only several years ago and the limited available literature. Audiological efficacy is reported in a limited number of studies, in which mostly moderate results are presented [90-98]. Whether the market share of transcutaneous bone implants continues to grow within the field of bone implants will be dependent on upcoming developments of more powerful sound processors and advances in active transcutaneous options. Passive solutions, like the Baha® Attract and the Sophono®, present with audiological concerns

due to skin dampening as stated [99,100]. Of these two options, the Baha® Attract has the advantage of the possibility of connection of (recently available) more powerful sound processors, which as long as no feedback issues arise, can expand the indications of the device. Next to this, with the Baha® Attract the option remains to change to a percutaneous solution, when warranted by the deterioration in bone conduction thresholds or by other issues, like pressure related skin problems. On the other hand, (expected) soft tissue problems with a percutaneous device in selected patients (or challenges in providing daily care), implant loss or aesthetic issues could be reasons to change a percutaneous implant to a transcutaneous solution or to choose a transcutaneous system at initial implantation. Given the good results of percutaneous implants in most patients, this might however apply to a limited number of patients. Active transcutaneous options might take away some of the audiology restrictions. For the Med-El™ Bonebridge®, a comparable audiological capacity to the percutaneous implant with standard (non-super-power) bone conduction devices is reported [101,102]. The preclinical and first clinical results on the Swedish Bone Conduction Implant were promising, with comparable results to those of the Bonebridge® [103-106]. Further clinical results should be awaited for this device, which will be commercially available in the near future as the Sentio from Oticon™. Another active system, the Cochlear™ OSIA system, is currently evaluated in a first trial, from which no results are published yet.

Although active solutions and more powerful sound processors might expand the possibilities for transcutaneous systems, other advantages of percutaneous bone implant will remain. The straightforward surgical implantation of the percutaneous bone conduction hearing implants with good clinical results of minor and infrequent complications is a major advantage. The surgery for percutaneous implants (linear incision with tissue preservation) is shorter in duration and is easily done under local anaesthesia. The less invasive procedure of percutaneous devices has some additional advantages, like considerably less soft tissue damage that can be important in case of future auricular reconstruction (provided they are placed in the correct position), and a more simple removal of the system, which might be necessary for various reasons. MRI compatibility is another important aspect to consider. Percutaneous implants are MRI compatible, transcutaneous implants are generally MRI conditional only up to 1.5 Tesla [107,108]. Moreover, scattering from the implant is far more extensive in the transcutaneous implants, up to 15 centimetres, compared to the scattering of percutaneous implants, up to 1 cm from the implant [107,109,110]. Patients who are likely to need frequent MRI may be less suitable for a magnetic transcutaneous option [111]. Based upon these advantages, percutaneous bone implants are expected to remain an important part of bone conduction hearing solutions in the near future. The continuous expansion and improvement of options for bone conduction hearing, including the current introduction of new active transcutaneous devices, is deemed important considering the increased possibility of patient-centered and individualized care.

Concluding remarks

This thesis emphasizes the importance of clinical evaluation of bone conduction hearing implants, for established percutaneous systems, as well as for new implants and surgical techniques. Preferably these innovations should be assessed on safety issues as well as on effectiveness and efficacy before widespread commercial implementation. Controlled trials, comparing new implants to the current gold standard, the percutaneous bone conduction hearing implant, are warranted. Newly available guidelines and the development of an (inter)national registry are expected to be of aid. Future research should include focus on prospective evaluation on specific indications and on preoperative identification of good candidates for bone implants in more detail. In this respect, separate evaluations of clinical outcome in paediatric populations are essential. The present focus on evaluation of new implant systems and more powerful sound processors is expected to remain a part of upcoming research. It is expected that for the foreseeable future, the percutaneous bone conduction hearing implant will remain an important addition to all available hearing rehabilitation options, and that current and new options contribute to more patient-centered and individualized care.

Summary

After an introduction on bone conduction hearing and the bone conduction hearing implant, the first part of this thesis (chapters 2-4) concentrates on the evaluation of several outcomes in clinical practice.

Chapter 2 presents the results of a study aiming to determine the relation between occurrence of complications of percutaneous implants and comorbidity factors. The rate of soft tissue reactions, revision surgery and implant loss is evaluated in light of the presence or absence of a variety of comorbidity factors. A large cohort of 581 adult patients with long term-follow-up (total of 7120 person years) was analysed with a proportional hazards regression model to identify associative factors for complications. For soft tissue reactions, skin disease could be identified as an independent risk factor. In a univariate analysis, fewer revisions were observed in the female gender and cardiovascular disease group. In multivariable analysis female gender and smoking were identified as negative risk factors for revision surgery. Smoking was identified as a risk factor for implant loss in both univariate and multivariable analysis. Previously identified risk factors, as BMI (body mass index) and diabetes, could not be confirmed in the current study. Outcomes were evaluated in this historical cohort, however, it should be noted that the implant and surgical technique used are infrequently used nowadays.

In chapter 3 the results of a new type percutaneous implant are described, applied in 79 children from two tertiary referral centers in Europe. This study was initiated because of a possible increased number of soft tissue reactions in the paediatric patient population. The mean follow-up was 11.7 months. The study could confirm a good implant survival (96.5% implant survival) and a rather stable rate of adverse soft tissue reactions over time was recorded. In contrast, soft-tissue reactions in adult patients using this same implant, decreased compared to previous generation implants (see Chapter 5). Additionally, an increase in revision surgery frequency was evident; in 28.7% of the implants one or multiple revision surgeries were required because of soft tissue problems (skin overgrowth). This increase resulted in more visits and a higher burden for the patients, family and health-care system. The study set-up (with missing control group) unfortunately hindered a firm conclusion on the cause for this increase. Additional studies are needed on this specific topic.

Chapter 4 focuses on an audiological outcome parameter, namely directional hearing in patients provided with bilateral bone implants. Children with bilateral conductive hearing loss were invited to take part in this study; eleven children participated. An outspoken effect of bilateral versus unilateral device use was seen, although this was mainly the result of (correct) lateralization of sounds rather than precise localization of the sound source in

the bilateral condition. In other words, these children can distinguish sounds coming from the left or the right side, without being able to indicate the exact sound source location. It should be noted that all children but one had congenital conductive hearing loss. The only child with acquired conductive hearing loss was by far the best performer, suggesting that previous 'normal' hearing experience during early childhood might be essential for good localization. From this study it was concluded that a second bone conduction device (BCD) is of importance to children with bilateral conductive hearing loss.

The second part of this thesis is composed of several chapters discussing new percutaneous implants, implant systems or new surgical techniques. In chapter 5, long-term data of a randomized controlled trial are presented, studying a new type of implant in adults. This new implant produced by Cochlear™ has a different shape of the abutment and wider diameter of the implant as compared to the older implant. A significant decrease in soft tissue reactions (2.5% versus 23.5% Holgers grade 2 reactions) and higher implant stability quotient (ISQ) was noticed with the new implant. However, no difference was noticed in increase in ISQ from baseline between the two implants. High implant survival rates were observed in both groups (96% versus 95%). Long-term evaluation after introduction of new implants is of importance. As an example, an unexplained drop in average ISQ values was recorded between 2 and 3 years follow-up, which was not reflected in the stability quotients of the implant in the current evaluation. The observed positive outcomes of this trial support the replacement of previous generation percutaneous implants by the new BI300 implant in adult patients.

In chapter 6 the results of an early post-market release study of another percutaneous implant are presented. Six months results of the first wide implant from Oticon Medical™ are evaluated and discussed. This study focussed on the ISQ and on implant loss, comparing the new test implant with the previous generation control implant. Fifty-seven adult patients with 60 implants were included in the trial, with a randomization ratio of 2:1 (test versus control). The test implant showed a significantly higher ISQ value compared to the control implant. Furthermore, the mean change in ISQ low during the trial was significantly larger for the test implant. No implants were lost and other clinical outcomes like the number of complications and adverse soft tissue reactions were comparable between test and control implants. These short-term results suggest that the new implant is a safe and good option in hearing rehabilitation. This study was continued; 3 years follow-up data are gathered and will be published soon.

For many years, implantation of percutaneous implants included a reduction of soft tissue at the implant site. It was assumed that a thin, rather immobile skin around the abutment was essential to reduce soft tissue infections. However, one of the leading centers in bone

implant research had introduced a simplified surgical procedure without skin reduction. In chapter 7 this tissue preservation technique was studied comparing the results of newly treated patients with published data of patients using the tissue reduction technique (as the 6-month data discussed in chapter 6). The results of this new technique were generally adequate, including comparable audiological results and a shorter surgery time (mean 25 minutes versus 32 minutes, $p<0.001$). However, during the first 6 months, an increase in soft-tissue reactions was observed in the soft tissue preservation group ($n=7$ versus $n=1$, $p=0.049$). The increase in adverse soft-tissue reactions was not evident in other studies, and the soft-tissue preservation technique is nowadays widely adopted as the new standard surgical method. Three-year results of our study are expected shortly.

Chapter 8 presents the results of a post market release study of a novel transcutaneous implant system. The system was evaluated in 54 patients regarding clinical outcomes, patients' opinions and audiological data. The audiological results were compared to a condition with a BCD on softband and the unaided condition, in a within patient design. The studied transcutaneous system is a so-called passive system, which suffers from less efficient sound transmission compared to percutaneous devices. On the other hand, the advantages of the closed skin include no need for daily care and less risk of implant loss and infection. These theoretical (dis)advantages were evaluated in the current multicentre trial. Post-operative soft tissue problems, like numbness and pain/discomfort at implant site, were reported rather frequently by the patients (21% numbness and 38% (slight) pain/discomfort at 6 months). On the predefined primary outcome parameter, the mean free-field hearing thresholds at 500-1000-2000-4000Hz, an improvement was observed compared to unaided hearing for the patients with conductive/mixed hearing loss, and for the patients with single sided deafness. The audiological tests were performed with the non-test ear blocked. Improvements compared to unaided hearing were also observed for speech tests in quiet and noise for the conductive/mixed hearing loss group and for speech in quiet in the SSD group. Good results were reported on subjective benefit questionnaires. In both groups, hearing performance was similar to results with the same sound processor connected to a softband, suggesting that this new transcutaneous implant performed similar to a (non-surgically) transcutaneous temporary application. For patients that require more amplification, because of a significant (high-frequency) sensorineural component in their hearing loss or single-sided deafness, the less efficient sound transmission could pose problems, and a more restrained recommendation was suggested. The multicentre design and the pre-selected indications provided a challenge and resulted in deviations in the protocol and difficulty in interpreting some of the results. It was concluded that a softband trial is a good preoperative indicator. Long-term results need to be awaited for proper selection of patients for either a transcutaneous or a percutaneous bone conduction implant.

In the current thesis a variety of topics within the field of bone conduction hearing implants were studied and discussed. Some of the recent developments in percutaneous and transcutaneous bone implants, new surgical techniques and clinical outcomes were evaluated. This thesis contributes to the assessment of a diverse set of trends in the field. The trends discussed will evolve and undergo further evaluation in the coming years.

Samenvatting

In hoofdstuk 1 wordt het concept beengeleiding en het beengeleidingsimplantaat toegelicht. Hierna spitst het eerste deel van dit proefschrift zich toe op de evaluatie van verschillende uitkomsten in de klinische praktijk.

In hoofdstuk 2 worden de resultaten van een studie beschreven, die de relatie tussen het optreden van complicaties bij percutane beengeleidingsimplantaten en comorbiditeitsfactoren onderzoekt. Het aantal huidreacties, revisie-operaties en implantaat verlies worden gerelateerd aan de aan- of afwezigheid van comorbiditeitsfactoren. Een groot cohort met 581 patiënten met lange termijn follow-up (totaal 7120 persoonsjaren) werd geanalyseerd met een proportioneel risico regressie model, met als doel het opsporen van geassocieerde factoren voor complicaties. Voor huidreacties werd een voorgeschiedenis met huidziekte geïdentificeerd als een onafhankelijk voorspellende factor. In een univariate analyse werden hiernaast minder revisie-operaties gezien onder vrouwelijke patiënten, en bij patiënten met een voorgeschiedenis van hart- en vaatziekten. In multivariabele analyse bleken het vrouwelijk geslacht en roken een negatief voorspellende waarde te hebben voor latere revisie-operaties. Roken bleek een positief voorspellende factor voor implantaat verlies in beide analyses. In eerdere studies gevonden factoren van invloed, zoals BMI (body mass index) en diabetes mellitus, konden in deze studie niet worden bevestigd als geassocieerde factoren. De uitkomsten werden gevonden in een historisch cohort, hierbij moet worden aangetekend dat de implantaten en chirurgische techniek in dit historische cohort in de huidige klinische praktijk nog weinig gebruikt worden, maar grotendeels vervangen zijn door nieuwe implantaten en technieken met een gunstiger postoperatief beloop.

In hoofdstuk 3 worden de resultaten van een nieuwer type percutaan beengeleidingsimplantaat beschreven onder 79 kinderen geopereerd in twee tertiaire zorgcentra in Europa. De studie werd gestart naar aanleiding van een klinisch opmerkelijke toename van huidreacties in de pediatrische patiëntpopulatie, welke gepaard ging met de introductie van een nieuw implantaat. De gemiddelde follow-up was 11,7 maanden. De studie bevestigde een goede implantaat overleving (96,5%) en toonde een nagenoeg stabiel aantal klinisch relevante huidreacties. Deze laatste bevinding moet in perspectief gezien worden van een eerdere studie, waarbij onder volwassen patiënten een afname van huidreacties vergeleken met het vorige generatie implantaat werd waargenomen (zie hoofdstuk 5). In de huidige studie werd hiernaast een toename van revisie-operaties in de pediatrische populatie gezien; in 28,7% van de implantaten bleken er 1 of meerdere revisie-operaties nodig in verband met huidproblemen (huid overgroei). Deze toename resulteerde in meer ziekenhuisbezoek en toegenomen belasting voor patiënten, familie en het zorgsysteem.

De onderzoeksopzet (met ontbrekende controle groep) verhinderde harde conclusies over de achterliggende oorzaak van deze toename, hiervoor zijn aanvullende studies vereist.

Hoofdstuk 4 behandelt de uitkomsten aangaande richtinghoren in een groep van kinderen met tweezijdige aanpassing met beengeleidingsimplantaten. Kinderen met bilateraal conductief gehoorverlies werden uitgenodigd om mee te doen aan deze studie, en 11 kinderen stemden in met deelname. Een uitgesproken voordeel van bilateraal versus unilaterale aanpassing werd gezien in de richtinghoren testen. Dit was echter gebaseerd op correcte lateralisatie van geluid en niet op basis van exacte lokalisatie van de geluidsbron in de bilaterale conditie. Met andere woorden, deze kinderen waren in staat een goed onderscheid te maken of geluiden van links of rechts werden aangeboden, zonder de precieze locatie van het geluid te identificeren. Hierbij moet nog worden aangetekend dat het bij 10 van de 11 kinderen een congenitaal bilateraal gehoorverlies betrof. De deelneemster met een verworven bilateraal conductief gehoorverlies was met afstand de beste in het exact lokaliseren van het geluid, waarbij het vermoeden zou kunnen ontstaan dat vroegtijdige bilaterale ervaring essentieel zou kunnen zijn voor goede lokalisatie van geluid. Uit de resultaten kan worden geconcludeerd dat een tweede beengeleidingsimplantaat van grote meerwaarde is voor kinderen met bilateraal conductief gehoorverlies.

Het tweede deel van dit proefschrift is een samenstelling van verschillende studies naar nieuwe implantaten en chirurgische technieken. In hoofdstuk 5 wordt lange termijn data van een gerandomiseerde studie beschreven, waarin een nieuw type implantaat van Cochlear™ wordt onderzocht onder volwassen patiënten. Dit nieuwe implantaat kent een andere vorm van het koppelstuk en grotere diameter van het implantaat vergeleken met het oude implantaat. Een significante afname in huidreacties (2,5% versus 23,5% Holgers graad 2 reacties) en hogere implantaat stabiliteits quotient (ISQ) werden gevonden. Er kon geen verschil worden gevonden in toename van deze ISQ ten opzichte van de uitgangswaarde tussen beide implantaten. Hoge overlevingspercentages werden genoteerd voor beide groepen (96% versus 95%). Het belang van lange termijn evaluatie na introductie van nieuwe implantaten werd duidelijk nadat er in deze studie op een eerder gevonden afname in ISQ tussen 2 en 3 jaar follow-up, geen verdere daling kon worden vastgesteld. De goede uitkomsten van deze trial ondersteunen de vervanging van de vorige generatie implantaten door het nieuwe BI300 implantaat in de volwassen patientenpopulatie.

In hoofdstuk 6 worden de eerste resultaten van een studie naar een ander percutaan implantaat gepresenteerd, namelijk de 6 maanden uitkomsten van het eerste bredere implantaat van Oticon Medical™. Deze studie richtte zich met name op ISQ en implantaatverlies, waarbij het nieuwe en bredere test implantaat vergeleken wordt met het vorige generatie implantaat van Oticon Medical™. Zevenenvijftig volwassen patiënten met 60

implantaten werden in de studie geïncludeerd, met een randomisatie ratio van 2:1 (test versus controle). Het testimplantaat toonde een significant hogere ISQ waarde vergeleken met het controle implantaat. Hiernaast was de gemiddelde toename in de lage ISQ significant verschillend tussen de beide groepen, in het voordeel van de testgroep. In geen van de groepen gingen implantaten verloren, en andere klinische uitkomsten, zoals het aantal complicaties en relevante huidreacties, waren vergelijkbaar tussen de twee groepen. Deze korte termijn resultaten suggereren dat het nieuwe implantaat een goede optie is onder de diverse huidige percutane implantaten. De studie wordt voortgezet tot 3 jaar en de resultaten van deze langere follow-up verschijnen binnenkort.

Gedurende lange tijd was uitdunning van weke delen rond het implantaat een vast onderdeel van de chirurgische techniek waarmee percutane implantaten worden geplaatst. Het werd aangenomen dat een dunne, relatief weinig mobiele huid rond het koppelstuk een belangrijke factor was in het voorkomen van postoperatieve huidproblemen. Echter, werden er door een ander centrum eerste resultaten vermeld van een nieuwe chirurgische techniek waarbij deze huidreductie stap werd overgeslagen. In hoofdstuk 7 wordt deze weefselsparende techniek bestudeerd en de resultaten van patiënten geopereerd met deze nieuwe methode vergeleken met resultaten van patiënten in een eerdere studie (beschreven in hoofdstuk 6). De resultaten van deze nieuwe techniek bleken over het algemeen adequaat, met vergelijkbare uitkomsten op audiologisch gebied; met hierbij een reductie in operatietijd (25 versus 32 minuten, $p<0.001$). Echter, gedurende de eerste 6 maanden, werden er in onze studie meer huidreacties geobserveerd in de weefselsparende techniek ($n=7$ versus $n=1$, $p=0.049$). De toename van huidreacties was niet evident in andere studies nadien en de weefselsparende techniek is tegenwoordig breed toegepast als standaard chirurgische methode. De resultaten van onze studie na 3 jaar worden binnenkort verwacht.

Hoofdstuk 8 beschrijft de uitkomsten van een studie naar een nieuw transcutaan implantaat systeem van Cochlear™. Dit systeem werd geëvalueerd in 54 patiënten waarbij gekeken werd naar klinische resultaten, audiologische gegevens en het (subjectieve) oordeel van patiënten. De audiologische uitkomsten werden vergeleken met een situatie met een beengeleidingstoestel op een softband en een ongeholpen situatie binnen elke patiënt. Het bestudeerde systeem is een zogenaamd passief transcutaan systeem, welke gepaard gaat met een minder efficiënte geluidsoverdracht vergeleken met percutane systemen. Aan de andere kant kent een transcutaan systeem voordelen, zoals geen dagelijkse zorg van de huid en minder risico op huidinfectie en implantaatverlies. Deze voor- en nadelen waren onderwerp van studie in hoofdstuk 8. Postoperatieve huidproblemen, zoals gevoelloosheid en pijn/discomfort rond het implantaat, werden relatief vaak genoemd door de deelnemende patiënten (21% gevoelloosheid en 38% (enige) pijn/discomfort na 6

maanden). De vooraf gekozen primaire uitkomstmaat, de gemiddelde drempel in het vrije veld op 500-1000-2000-4000Hz, toonde een verbetering met het implantaat vergeleken met een ongeholpen situatie voor patiënten met conductief of gemengd gehoorverlies, en voor patiënten met single-sided deafness (SSD). Deze testen werden uitgevoerd met het niet-aangedane oor geblokkeerd. Verbeteringen vergeleken met de ongeholpen situatie werden ook waargenomen in de spraak in stilte en spraak in ruis testen voor de conductief/gemengd gehoorverlies groep en de voor spraak in stilte test in de SSD groep. Hiernaast werden goede resultaten waargenomen op de vragenlijsten. De uitkomsten van het nieuwe implantaatsysteem bleken over het algemeen vergelijkbaar met de situatie met het beengeleidingsimplantaat gedragen op een softband. Voor patiënten die meer versterking nodig hebben, bijvoorbeeld door een significante perceptieve component in het gehoorverlies of in geval van SSD, kan de minder efficiënte geluidsoverdracht problemen geven, en wordt een beperktere indicatiestelling geadviseerd.

De multicenter opzet van de studie, en de vooraf geselecteerde verschillende indicatietypen resulteerde in uitdagingen in de analyse van de data en soms lastig te interpreteren resultaten. Geconcludeerd kan worden, dat de proef met een beengeleidingsimplantaat op softband een goede preoperatieve indicator is van het uiteindelijke audiologische resultaat. Lange termijn resultaten moeten worden afgewacht voordat criteria voor juiste selectie van patiënten voor dergelijke implantaten kunnen worden vastgesteld.

In dit proefschrift worden uiteenlopende onderwerpen binnen de beengeleidingsimplantaten bestudeerd en bediscussieerd. Enkele van de recente ontwikkelingen in percutane en transcutane implantaten, nieuwe chirurgische technieken en klinische uitkomsten worden geëvalueerd. Dit proefschrift draagt hiermee bij aan de beschrijving van de ontwikkelingen op het gebied van beengeleidingsimplantaten. De besproken ontwikkelingen zullen naar verwachting de komende jaren verder evolueren en verder analyse ondergaan.

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Appendices

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Curriculum Vitae

Christine den Besten was born on 11 June 1987 in Harmelen, the Netherlands. After completing high school (VWO, Minkema College, Woerden) in 2005, she started studying medicine at Leiden University. During her studies and internships she developed an interest in surgery of the head and neck. In 2012 she finished her internships and obtained the medical degree (cum laude). After graduating medical school she worked as a house oficer at the general surgery department of the MC Haaglanden for a year before deciding on a career in otolaryngology. In September 2013 she started a PhD trajectory on bone conduction hearing implants resulting in this thesis. In December 2015 she started her training as an oolaryngology resident at the Radboudumc. Part of her training was completed at the oolaryngology department of the Rijnstate hospital in Arnhem. Currently she is working as a resident in the Radboudumc again.

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