PERCUTANEOUS BONE-ANCHORED HEARING SYSTEMS

EVALUATING THE STATE OF THE ART, INVESTIGATING NEW DEVELOPMENTS AND EXPLORING CLINICAL CHALLENGES

COOSJE J.I. CASPERS

Percutaneous bone-anchored hearing systems

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Coosje J.I. Caspers
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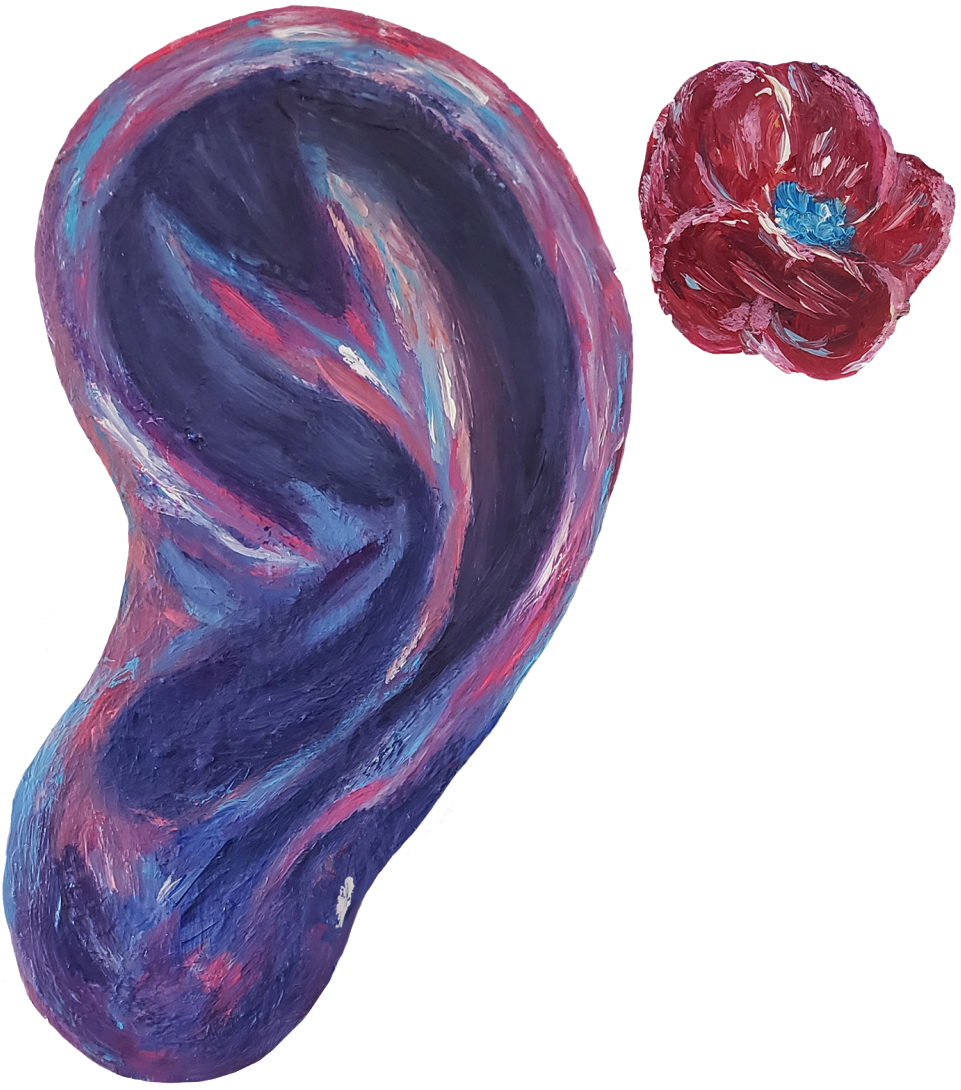

CHAPTER 1

General introduction and thesis outline

Although suffering from progressive hearing loss, Ludwig van Beethoven was a successful musician in the 18th century. Nowadays, this German pianist is considered to be one of the greatest composers of all time. In order to compose music, the hearing-impaired Beethoven placed a wooden stick between his teeth and the piano, enabling him to hear sounds through *bone conduction*. (1) With bone conduction hearing, acoustic vibrations travel through the skull bone to the inner ear. The inner ear converts these vibrations into electrical signals that are sent to the brain, allowing us to perceive sounds. (2)

Since the 19th century, the principle of bone conduction has been applied in various types of hearing aids, eventually leading to the implantation of the first percutaneous bone-anchored hearing implant (BAHI) system in 1977. (3) Over the past decades, this implant system has evolved into a well-established hearing rehabilitation method which is used in a broad range of hearing-impaired patients who cannot benefit from surgery or conventional hearing aids. (4-6)

This thesis evaluates long-term results of the current percutaneous BAHI systems and investigates new developments within this field. In order to interpret the outcomes of the present thesis, it is of importance to understand the basic concepts of hearing and bone conduction implant systems. Below, these topics are described into more detail.

Anatomy and physiology of the auditory system

Hearing is the process in which the inner ear or cochlea transforms mechanical vibrations into nerve impulses that are subsequently sent to the brain via the auditory nerve. The auditory cortex processes these nerve impulses and translates them into sounds. There are two distinct pathways for converting acoustic stimuli into cochlear vibrations: the air conduction and bone conduction pathway.

The air conduction pathway is the primary and most efficient pathway in a normal hearing person. (8) This pathway comprises the outer ear and middle ear (figure 1). The outer ear consists of the pinna and the external auditory canal and is separated from the middle ear by the tympanic membrane. The pinna collects sound waves and directs them through the external auditory canal to the tympanic membrane. With its characteristic shape, the pinna selectively changes the frequency profile of sound stimuli and thus provides spectral cues used for localization in the vertical plane. (9) The tympanic membrane transforms sound waves into mechanical vibrations that are conducted along the three ossicles in the middle ear (malleus, incus and stapes), to the oval window of the cochlea. The cochlea is a spiral-shaped cavity which consists of three fluid-filled ducts or scalae. The scalae vestibuli and tympani contain perilymph and the scala media is filled with endolymph. The scale vestibuli extends from the oval window to the apex of the cochlea

(helicotrema), where it continues as the scala tympani until the round window. The scala media is located between the scalae vestibuli and tympani, separated from these ducts by Reissner's membrane and basilar membrane, respectively. In the scala media, the organ of Corti is situated on the basilar membrane. This organ contains hair cells with stereocilia that convert motion into neural signals. Mechanical vibrations arriving at the oval window result in movement of the perilymph inside the scalae vestibuli and tympani causing the basilar membrane to vibrate. Due to these vibrations, the stereocilia of the hair cells are deflected leading to a depolarization of the hair cell and subsequent excitation of the dendrites of the auditory nerve. Subsequently, nerve impulses are transmitted via the auditory nerve to the brain. When sounds are transmitted by bone conduction, a similar conversion process is induced inside the cochlea, transforming mechanical vibrations into nerve impulses. (10) The bone conduction pathway transmits sound waves via the skull bones to the cochlea leading to excitation of the basilar membrane. The exact physiology behind bone conduction hearing is not yet fully understood, but several contributing factors have been identified. (11) The most important factor is the conversion of skull vibrations into a perilymph flow between the scalae vestibuli and tympani due to the inertia of cochlear fluids. Other possible contributing factors are inertia of the ossicles in the middle ear, sound radiation in the external auditory canal and compression of the cochlear walls. (12)

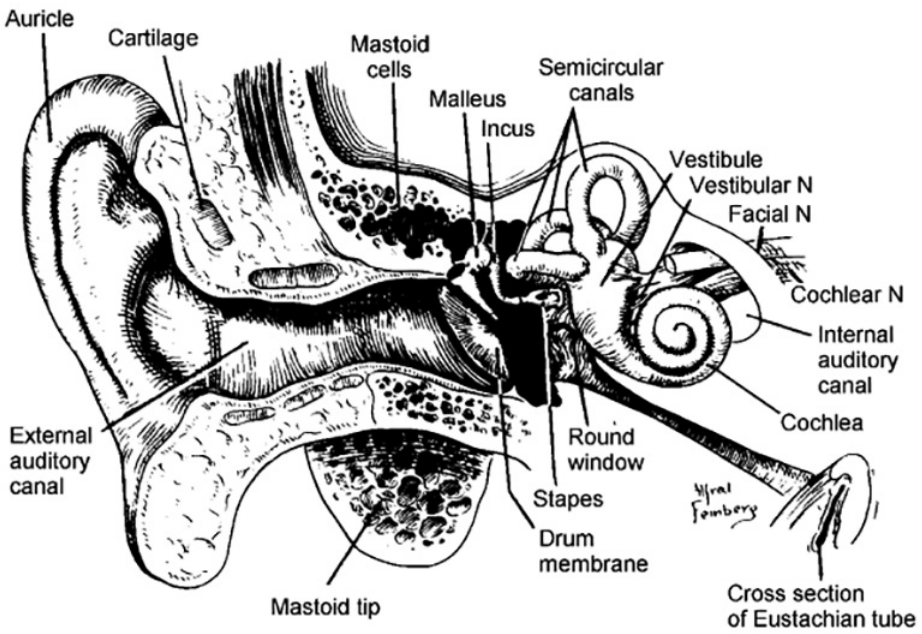

Figure 1. Anatomy of the middle and inner ear

Figure originally published by Davis and Silverman (7)

The bone conduction pathway bypasses the outer and middle ear. As such, sound transmission through bone conduction is 40-70 dB less effective when compared with transmission by air conduction. (8) A normal hearing person therefore mainly depends on air conduction for auditory perception. However, in cases where the air conduction pathway is blocked, for instance due to an ear infection or congenital atresia, the bone conduction route may prove useful. Especially when acoustic signals are applied directly to the skull bones or teeth. Thereby, the inefficient bone conduction pathway becomes much more effective in terms of sound transmission. (13) Direct stimulation can for instance be achieved by placing a vibrator on the skull bone or teeth. This mechanism was used in the development of the bone-anchored hearing implant system.

Hearing loss

The normal physiology of hearing is described in the previous paragraph. Unfortunately, disorders of the auditory system are quite common, with 5% of the world's population suffering from disabling hearing loss resulting in associated global costs of $750-790 billion a year. (14) Hearing loss can occur unilaterally or bilaterally and may already be present at birth (congenital), or can be acquired later in life. In general, three types of hearing-impairment can be distinguished: sensorineural hearing loss (SNHL), conductive hearing loss (CHL) and mixed hearing loss (MHL). SNHL is caused by cochlear or retrocochlear dysfunction and is the most common type of hearing loss. CHL results from problems in the outer and/or middle ear, such as chronic ear infections or anatomic malformations. In case of MHL, both a conductive and sensorineural component are present.

Now that we have learned more about the physiology behind hearing loss, we can deduce that Beethoven must have suffered from a condition resulting in CHL: Beethoven was able to hear sounds only via bone conduction, suggesting sufficient function of the cochlea and an abnormal function of the outer and/or middle ear. On the other hand, Beethoven also reported symptoms such as tinnitus and decreased speech in noise, which are not only associated with CHL, but also with SNHL. Furthermore, with time, hearing loss progressed until Beethoven was completely deaf at the age of 52. (15) Most likely, Beethoven thus suffered from MHL with a progressive sensorineural component. (15) After Beethoven's death in 1827, autopsy was performed on his body in order to retrieve the etiology of his hearing loss. Based on this autopsy report, and on Beethoven's correspondence, several causes for his hearing loss have been suggested, varying from syphilis to otosclerosis. (15-18) Unfortunately, these suggested etiologies just remain hypotheses en we will probably never know what exactly caused Beethoven's hearing impairment. We cán however fantasize about the possible hearing rehabilitation methods that we could have offered Beethoven if he had lived today. In the paragraph below, hearing rehabilitation methods are described.

Hearing rehabilitation

Patients with SNHL are usually rehabilitated with conventional hearing aids, or in selected (and progressive) cases, with a cochlear implant. In patients with CHL or MHL, the two main hearing rehabilitation methods are surgical reconstruction and air conduction hearing aids. Unfortunately, reconstructive surgery is not feasible in every patient and in some patients conventional hearing aids cannot be applied due to, for instance, anatomic malformations or recurrent ear infections. In these patients, a BAHI system is a good alternative to restore hearing. A BAHI system captures acoustic stimuli and transforms these into mechanical vibrations resulting in vibrations of the temporal bone which establishes excitation of the basilar membrane within the cochlea. (4-6) As such, sufficient cochlear function (bone conduction thresholds <60 dB for the better hearing ear) is required, in order to benefit from a BAHI. (4,19) A BAHI is therefore not indicated in patients with severe bilateral SNHL. However, the percutaneous BAHI system can be used in cases of unilateral SNHL. In these patients, the percutaneous BAHI transmits acoustic stimuli from the hearing-impaired side to the normal functioning contralateral cochlea, thereby creating a benefit in specific listening situations. (20-22)

Bone-anchored hearing implants

As previously mentioned, the first bone conduction hearing aid was already invented in the 19th century. These early bone conduction devices were mainly applied to the teeth. Later developments resulted in devices worn on a steal headband at the mastoid bone and devices incorporated in eyeglasses. The disadvantages associated with these devices, such as pressure-related skin problems and suboptimal sound transmission, led to the development of a skin-penetrating or percutaneous implant, anchored in the temporal bone. (23) This percutaneous bone-anchored hearing implant was invented by Tjellström and co-workers in 1977 and became commercially available in 1987. (24) Examples of a percutaneous BAHI system are shown in figure 2. The system comprises a titanium implant which is inserted into the mastoid bone behind the ear and a skin-penetrating titanium abutment which is attached to the implant. Externally, a sound processor is coupled onto the abutment. The sound processor captures sounds and transforms these into mechanical vibrations which are conducted via abutment, implant, and skull bone to the cochlea.

Besides the percutaneous BAHI system, transcutaneous BAHI systems are available as well. Transcutaneous systems leave the skin intact and can be divided into passive and active systems. (25) A passive transcutaneous systems consists of a sound processor with external magnet which transmits mechanical vibrations through the skin and subcutaneous tissue to an internal magnet placed onto the temporal bone. With an active system, an external sound processor transmits electromagnetic signals through the skin to a subcutaneously implanted active implant which then starts to vibrate.

As the current thesis focuses on percutaneous BAHI systems, transcutaneous systems will not be further discussed.

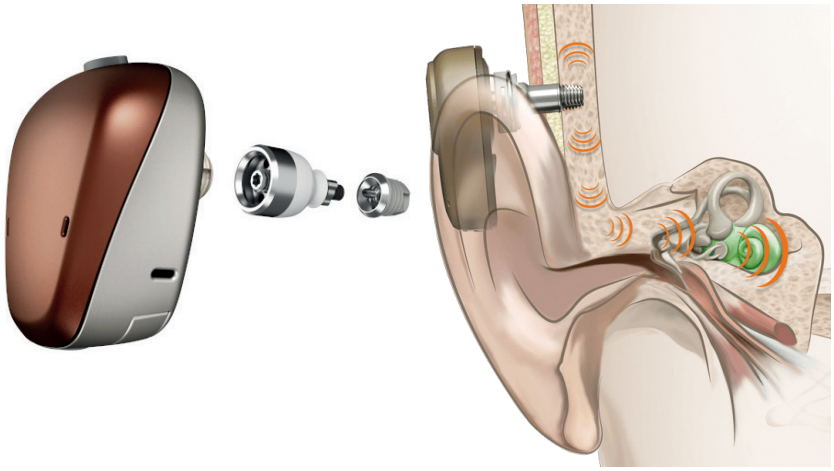

Figure 2. The percutaneous bone-anchored hearing implant system

The image on the left shows the three different parts (sound processor, abutment and titanium implant) of a percutaneous BAHI system. *Copyright Cochlear Limited. Reprinted with permission.* The image on the right shows an implanted BAHI system. *Image provided by Oticon Medical TM. Reprinted with permission.*

Developments in the field of percutaneous BAHI surgery

In our institution, the Radboud university medical center, Nijmegen, the Netherlands, the first BAHI system was implanted in 1988 by prof. dr. C.W.R.J. Cremers. Today, 33 years later, more than 2000 BAHI systems have successfully been installed in Nijmegen. Many developments in implant and abutment designs, surgical techniques and sound processors have occurred within this time-period.

During the early years of BAHI surgery, implantation was performed in two stages in order to obtain good osseointegration and thereby avoid implant loss. (26) A 3.75-mm-wide implant was inserted into the temporal bone in the first procedure, using a semicircular incision to elevate skin and periosteum. The skin was then closed. In a second procedure three to six months later, the skin was re-incised and a 5.5-mm long abutment was attached to the implant. Prior to skin closure with a free skin graft or U-flap, reduction of subcutaneous tissue and hair follicles was advocated according to the hypothesis that this would minimize the risk of peri-implant inflammation and skin-overgrowth. (27) Within one to four weeks after the second procedure, the sound processor was fitted. (27,28) In 1989, the two-stage procedure in adults was modified to a one-stage procedure in which the implant and abutment were implanted simultaneously. This one-stage technique showed comparable implant survival rates when compared to two-stage surgery and became the

new standard technique in adults. (29,30) To achieve successful osseointegration, sound processor fitting was advocated at approximately six weeks after one-stage surgery. (29,30) A couple years later, in the early 90's, a less invasive surgical technique was developed in the Radboud university medical center: the linear incision technique with soft tissue reduction (LIT-TR). (31) With its less invasive character, this technique resulted in shorter surgery time, faster wound healing and less (soft tissue) complications. (31-34) Despite these improvements, complications such as adverse skin reactions, implant loss, skin overgrowth and numbness were still a recurrent issue. In order to further reduce these complications, new implant and abutments were designed as well as refinements in surgical techniques. In 2003, a longer, 8.5-mm, abutment was manufactured which resulted in a greater distance between the rim of the abutment and the patient's skin as opposed to the regular 5.5-mm abutment. This 8.5-mm abutment was found useful in patients with recurrent skin infections, in patients with thick skin, and in cases of skin overgrowing the abutment. (35) In an attempt to reduce implant loss, a new implant, the so called 'wide diameter implant', was introduced to the market in 2010. This 4.5-mm-wide implant had a larger bone-implant contact surface when compared to its processor, the 3.75-mm-wide implant, and was found to be superior in terms of short-term implant stability and survival. (36-38) Because of the improved implant survival, it was thought to be safe to reduce loading time of the sound processor from six to three weeks postoperatively. Several studies indeed proved loading to be safe at three weeks in terms of implant loss and skin complications. (39,40) Together with these good implant survival rates and early loading, it also felt safe to start using longer abutments already at implantation, instead of replacing the abutment in case of skin problems.

In 2011, Hultcrantz modified the LIT-TR into a procedure without soft tissue reduction: the linear incision technique with soft tissue preservation (LIT-TP). (41) This new technique inflicted less surgical trauma to the soft tissue and thus resulted in a shorter surgery time, less numbness and better cosmetic outcomes when compared to the technique with soft tissue reduction. (41-43) Although the short-term outcomes of the LIT-TP, as well as the 4.5-mm-wide implant, seem promising, limited data is available on long-term outcomes. (44-46) In **chapter 2** of this thesis, one of the first long-term (i.e. 5 years) clinical outcomes of the 4.5-mm-wide implant and the LIT-TP are presented and compared to the 3.75-mm-wide implant and the LIT-TR, respectively.

In 2013, a new, even less invasive surgical technique was introduced (figure 3). This surgical punch procedure called minimally invasive Ponto surgery (MIPS) was designed to decrease surgery time, healing time and to reduce numbness and adverse skin reactions even more in comparison to the LIT-TP technique. (47) On the other hand, high implant loss rates with MIPS have been reported. (48-50) Before implementing this new procedure in clinical practice, a thorough evaluation of this technique and it's supposedly added value compared to the LIT-TP, is of importance. In **chapter 4 and 5** of this thesis, clinical outcomes of MIPS are evaluated and compared to outcomes of the LIT-TP.

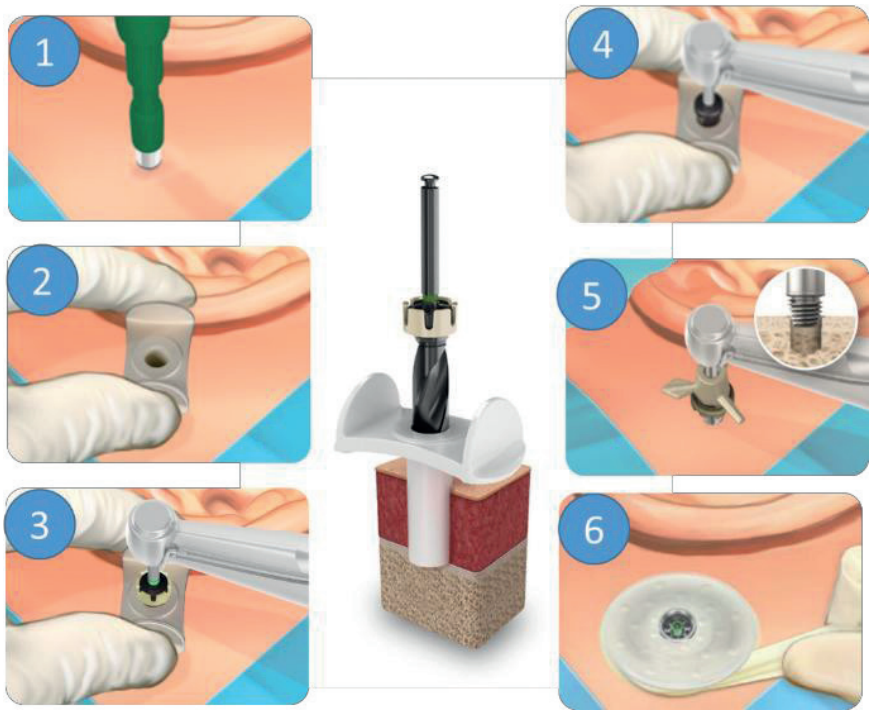

Figure 3. Minimally invasive Ponto surgery

The MIPS procedure is advocated as follows: (1) 5-mm biopsy punch is used to create a circular incision; (2) cannula is inserted; (3, 4) stepwise drilling is performed; (5) cannula is removed and the implant is inserted; and (6) healing cap with dressing is placed.

Image provided by Oticon Medical TM. Reprinted with permission.

Current practice in Radboud university medical center

The above mentioned developments, amongst others, resulted in a standard practice for BAHI care in the Radboud university medical center. In this center, patients indicated for a BAHI are implanted with a 4.5-mm-wide implant using the linear incision technique with soft tissue preservation (LIT-TP). If feasible for both clinician and patient, surgery is performed under local anesthesia (72% of our adult population). In children, surgery is performed under general anesthesia. From the age of 10, a one-stage procedure is conducted using the LIT-TP. Children below 10 years old are operated in two stages. In these children, a spare fixture (also called 'sleeper' implant) is placed during the first surgery which will be available in case the other implant will be lost in the future. After one-stage surgery, or after the second surgery in case of a two-stage procedure, a dressing with antibiotic ointment is placed onto the abutment. This dressing is removed at the first follow-up visit, seven days postoperatively. At this visit, patients are instructed to apply antibiotic ointment around the abutment twice a day, for two weeks. Loading of the sound processor is performed at three weeks

after one-stage surgery, or at one week after the second procedure in case of two-stage surgery. For every patient, a yearly checkup of the BAHI and surrounding soft tissue is planned.

Outcome measures

Safety and success of a BAHI system are evaluated on the basis of clinical outcomes. These outcomes include intraoperative complications, implant survival and stability, soft-tissue tolerability, skin sensibility, and pain. In addition to these clinical outcomes, audiological outcomes and measures such as patient satisfaction and quality of life evaluations are also important. Below, these outcome measures will be described into detail.

Intraoperative complications

With the development of less invasive surgical procedures, intraoperative complications rarely occur nowadays. Complications of BAHI surgeries performed between 2009 - 2020 in the Radboud university medical center consist of exposure of the dura mater, or bleeding from an emissary vein, dura or sinus. Bleeding can be easily resolved by inserting the implant into the drilled hole. An exposed dura is usually without any clinical consequences. However, rare complications such as subdural and epidural hematoma have been described. (51,52)

Implant survival and stability

Implant survival is one of the main outcome measures after BAHI surgery. Implant loss can occur spontaneous, or due to osseointegration failure, trauma or infection. In some cases, implants are electively removed because of persistent pain or infection. In the pediatric population, implant loss occurs more often than in the adult population, probably as a result of thinner cortical bone, more frequent head trauma and difficulty in maintaining peri-implant hygiene. (5,53) Within both populations however, a large variability in implant loss rates is observed, ranging between 1.6% and 17.4% in adult and mixed populations and between 0% and 25% in the pediatric population. (54) This variability can be explained by differences in surgical techniques and implant types, as well as by differences in patient characteristics. Known risk factors for implant loss are smoking, radiated bone at the implant side, mental retardation, and diabetes mellitus. (5,55-57) Unfortunately, most research on implant loss involves the previous generation 3.75-mm-wide implants. It is therefore unclear whether the above mentioned risk factors also apply to the currently used 4.5-mm-wide implants.

In an attempt to objectively measure implant stability, Meredith et al. developed the resonance frequency analysis (RFA). (58) With RFA measurements, a metal rod (Smartpeg) is attached to the abutment and excited by magnetic pulses from an Ostell device (Osstell AB, Göteborg, Sweden). The excitation of the SmartPeg results in vibrations of the implant-abutment system, which are

detected by the Ostell device. The devices converts the resonance frequency into the Implant Stability Quotient (ISQ). The ISQ ranges between 1 to 100 with a higher score indicating higher implant stability. ISQ values are measured in two perpendicular directions, resulting in an ISQ-high and ISQ-low. (59) Within clinical research, implant stability is usually determined by means of the ISQ. The added value of the ISQ lies in the measurement of the ISQ time course in individual patients, as this may reflect (changes in) implant stability. (60) In this thesis, ISQ measurements were conducted directly after surgery and at predefined time-points during follow-up. As the clinical implication of an individual ISQ value at a certain time point is unclear, ISQ measurements are currently only advocated for clinical research and not for clinical practice.

Soft tissue tolerability

After BAHI surgery, complications related to soft tissue surrounding the implant-abutment system can occur. Complications shortly after surgery comprise of pain, persistent bleeding, hematoma and minor wound dehiscence. These complications are rare, and if present, easily treatable. The main soft tissue complication which can occur at any moment after BAHI implantation, is an infection of the soft tissue surrounding the implanted system. These infections arise as a results of the skin-penetrating abutment which creates a permanent entry point for micro-organisms. In order to avoid soft tissue infections, hygienic care around the abutment is of utmost importance. Unfortunately, despite good care, soft tissue reactions still occur. Soft tissue reactions vary from mild to severe. Persistent infections can eventually lead to implant loss or removal. A grading system to classify the severity of soft tissue reactions was proposed by Holgers et al., in 1988 (table 1). (61) Holgers scores range between 0 and 4, with a Holgers score ≥ 2 considered to be an adverse skin reaction requiring treatment. In a recent systematic review evaluating adverse skin reactions after LIT-TP surgery, adverse Holgers scores were reported amongst all age groups and centers in 18% of implanted patients. (62) Although widely used, the Holgers scale has its limitations. The scale was originally developed to grade soft tissue reactions from three months after surgery and therefore lacks the assessment of wound healing and skin closure. In addition, clinically relevant parameters such as pain and skin height are not evaluated within the Holgers grading system. Furthermore, this scale only assesses skin status in percutaneous systems and is not applicable to transcutaneous systems. (63) Pain is an important parameter as it might result from an adverse skin reaction. Pain can however also be present without any signs of a clinical cause. (64,65) This so-called idiopathic pain is rare and often results in implant removal or loss due to the lack of an adequate treatment. (66-68) **Chapter 6** describes the clinical characteristics of 14 patients with idiopathic pain and proposes a treatment regimen for this burdensome complaint. Another important clinical parameter in postoperative BAHI care is skin height. Increased skin height can lead to infections and concomitant problems with sound processor coupling, which might eventually result in abutment change, abutment removal or revision surgery. (62,68)

Table 1. The Holgers classification (61)

Holgers grade	Clinical description and medical response
0	No irritation Epithelial debris removed if present
1	Slight redness Temporary local treatment
2	Red and slightly moist tissue, no granuloma formation Local treatment and extra controls
3	Reddish and moist and sometimes granulation tissue Revision surgery is indicated
4	Removal of skin-penetrating implant necessary due to infection
R	Removal of implant for reasons not related to skin problems

In order to overcome the limitations of the Holgers scale, Kruyt et al. developed in 2018 a new soft tissue assessment scale, the IPS scale (figure 4). (63) The IPS scale can be used to evaluate infection parameters, pain, and skin height and can be used directly after surgery in both percutaneous and transcutaneous systems. Since the IPS scale has not yet been validated, both the Holgers and the IPS scale are used to describe soft tissue status in the current thesis.

Skin sensibility

In the past, when soft tissue reduction techniques were used in BAHI surgery, skin sensibility was an important clinical outcome measure. With the current tissue preservation techniques, numbness has become less of an issue. (69,70) However, when evaluating new surgical techniques, it is of importance to assess whether skin sensibility is as excellent as with the LIT-TP. Therefore, skin sensibility and numbness are used as clinical outcome measures in the current thesis.

Audiological outcomes

The audiological efficacy of a BAHI can be determined by measuring speech recognition at 50, 60 and 70 dB SPL in a free field condition. (19) According to the Dutch bone conduction device guideline, a BAHI needs to improve the phoneme score obtained with NVA monosyllables at 50 or 60 dB SPL with at least 20%. When a second BAHI is fitted in a patient with bilateral hearing loss, speech recognition in noise and sound localization ability should also be determined. (19) Although a second BAHI is known to improve speech understanding in noise, hearing-related quality of life (HRQoL) and sound localization in patients with bilateral hearing loss (71-75), many patients are still unilaterally implanted (76,77). Also, despite the importance of good localization skills in everyday life, very little information is available about sound localization ability in bilaterally fitted patients. (72,73,78) **Chapter 7** of this thesis provides more insight into the sound localization performance in 15 bilateral BAHI users and explores methods to improve localization behavior in daily practice.

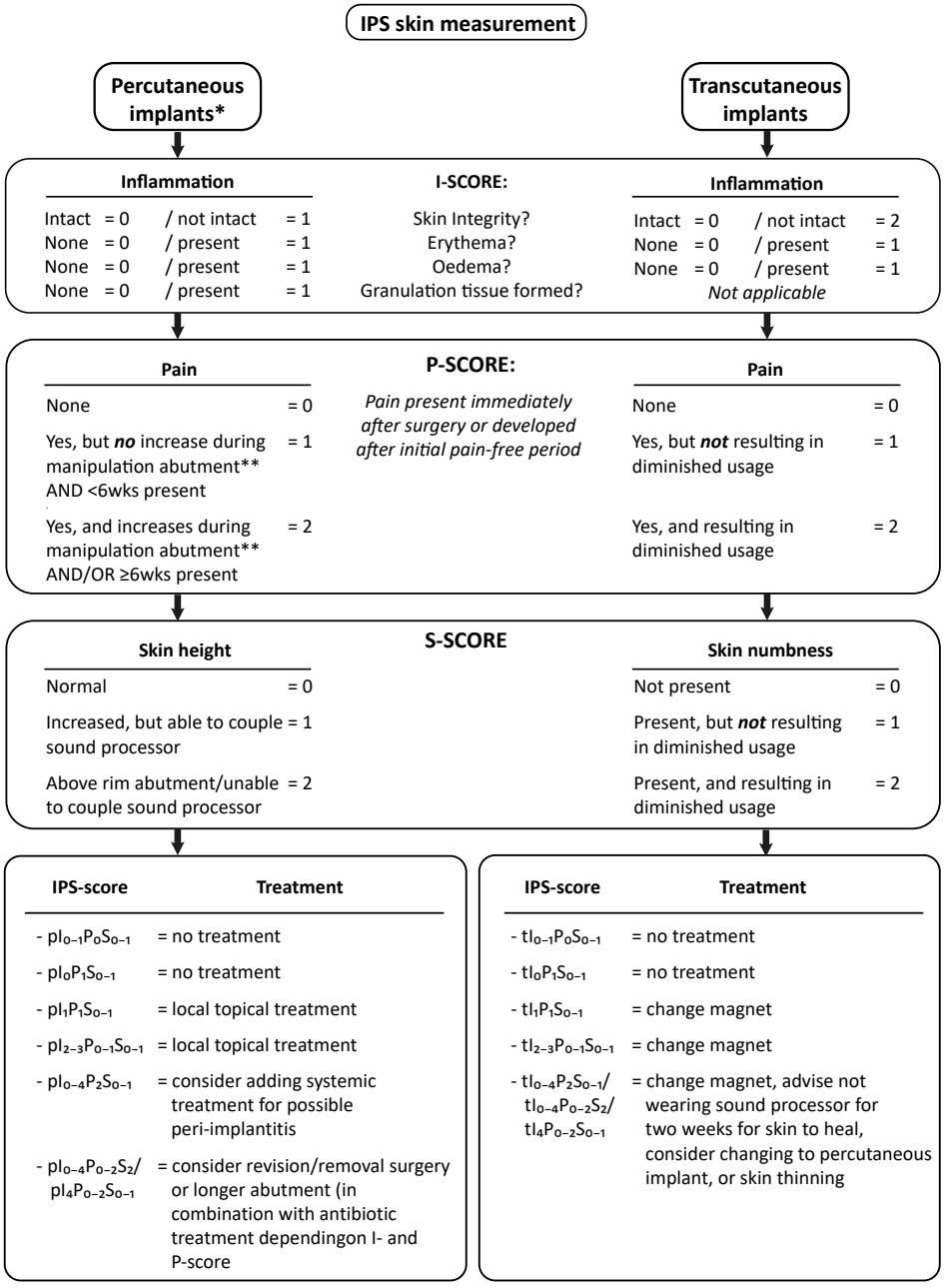

Figure 4. Flowchart of the IPS-scale and treatment advice

Figure originally published by Kruyt et al. (63)

Quality of life and efficacy of care

In addition to the above mentioned objective outcome measures, subjective outcomes such as quality of life (QoL) and patient satisfaction, are of major importance. First of all to ensure that patients indeed benefit from this intervention. Secondly, to justify the use of an implant system which involves both a surgical procedure and financial costs related to replacement of sound processors. (6,79,80) Unfortunately, generic QoL questionnaires do not seem sensitive enough to detect changes in general QoL in BAHI patients. (81) This contrasts strongly with our experiences in clinical practice with very satisfied BAHI users. **Chapter 3** of this thesis evaluates sound processor use and QoL, specifically related to hearing, in 75 patients with a BAHI. This evaluation comprises the Glasgow Benefit Inventory (GBI) questionnaire, the Glasgow Health Status Inventory (GHSI) questionnaire and sound processor use.

Patient satisfaction does not only involve satisfaction with the BAHI system itself, but with the entire process of care around it. Currently, new developments in the care process are proposed, such as loading the sound processor already one week after surgery instead of the standard of three weeks. Since a change in loading time would affect the patient, it is of importance to know the preference of these patients in terms of loading time. **Chapter 8** determines the preference of patients regarding their optimal loading time.

Scope and outline of this thesis

As mentioned before, previous research on BAHI demonstrates that the currently used systems and surgical techniques have improved postoperative outcomes when compared with previous systems and procedures. Unfortunately, little data is available on long-term clinical outcomes, long-term HRQoL and long-term sound processor use in patients treated according to the current clinical practice. The aim of the first part of this thesis is to close this knowledge gap.

In **chapter 2**, 5-year outcomes of the currently used 4.5-mm-wide implant and the LIT-TP are evaluated and compared with the previous generation 3.75-mm-wide implant and tissue reduction technique, respectively.

Chapter 3 provides more insight into HRQoL and sound processor use in 75 patients with a percutaneous BAHI. In this study, 3-year HRQoL outcomes and changes in HRQoL over time are investigated among and across different indication groups. Additionally, sound processor use is analyzed for different indications and correlation analyses between HRQoL and sound processor use are performed.

From the first part of this thesis, we have learned that postoperative outcomes for BAHI patients are favorable, but can still be further optimized. For instance, a minority of the patients with BAHIs still suffer from postoperative complications such as adverse skin reactions, numbness and idiopathic pain. The second and third part of this thesis therefore focus on optimizing BAHI outcomes and care. In **chapters 4 and 5**, a new surgical technique is evaluated, while in **chapters 6, 7 and 8** current clinical challenges are investigated and patient preferences are assessed.

In **chapters 4 and 5**, the added value of the new surgical procedure called MIPS is assessed by comparing clinical outcomes with the outcomes after the LIT-TP, the current gold standard procedure.

Idiopathic pain, a remaining clinical challenge in the field of BAHI surgery, is discussed in **chapter 6.** The clinical presentation and outcomes of 14 patients with idiopathic pain are retrospectively reviewed. Based on this evaluation, a treatment strategy for idiopathic pain is proposed.

In **chapter 7**, we evaluate sound localization performance in patients with bilateral BAHIs and investigate whether performance can be improved by optimizing the sound processor settings or by a localization practice session.

In view of patient-centered care, the patient perspective on optimal loading time after BAHI surgery is investigated in **chapter 8**.
Chapter 9 (general discussion), reflects on the main findings described in chapters 2-8 and discusses the relevance and implications of these findings. In addition, considerations for further improvements and future research within the BAHI field are given.

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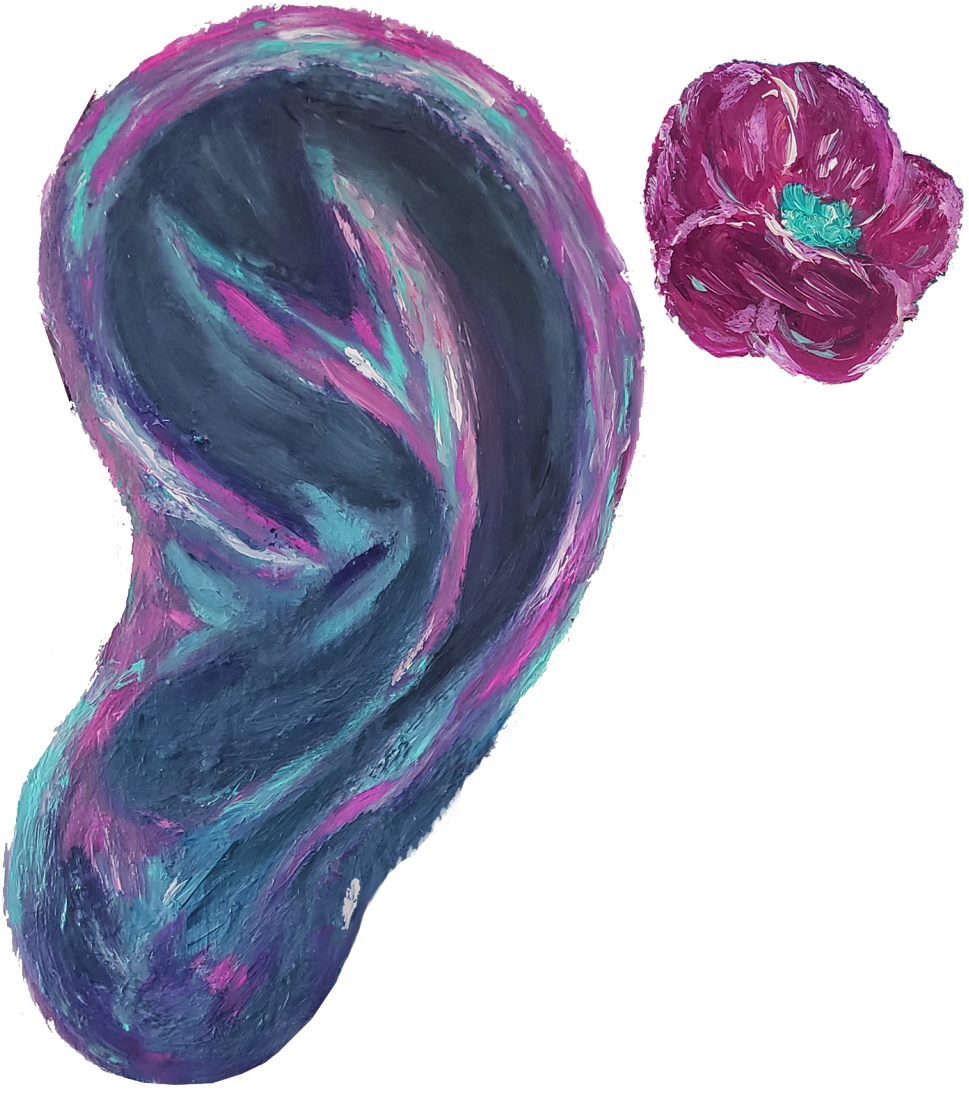
PART I

State of the art – clinical outcomes and hearing-related quality of life



CHAPTER 2

Long-term clinical outcomes of percutaneous implants for bone conduction devices: five-year evaluation of different implant designs and surgical techniques

Coosje J.I. Caspers and Maarten A. Vijverberg
Ivo J. Kruyt
Emmanuel A.M. Mylanus
Myrthe K.S. Hol

Under review *(Clinical Otolaryngology)*

Abstract

Purpose

To evaluate 5-year clinical outcomes of bone-anchored hearing implants. Outcomes were compared between a 4.5-mm-wide and a 3.75-mm-wide implant, as well as between the linear incision technique with soft tissue preservation (LIT-TP) and soft tissue reduction (LIT-TR).

Methods

Prospective single follow-up visit of two previously completed clinical studies. A total of 68 patients were included. These patients either received a 4.5-mm-wide or 3.75-mm-wide implant and were operated using either the LIT-TP or LIT-TR technique.

Results

No significant differences between the 4.5-mm-wide and 3.75-mm-wide implant were observed in implant- (97.4% versus 95.0%) or abutment survival (94.8% vs 95%). For the LIT-TP versus the LIT-TR, no significant differences between implant (96.0% vs 100%) or abutment survival (92.0% vs 92.0%) were seen. Implant stability quotient (ISQ) from surgery increased significantly over time for both implants and both surgical techniques. During the 5-year follow-up of patients operated using the LIT-TR, adverse Holgers scores (Holgers≥ 2) were observed in 15.2% of the 4.5-mm-wide implants and in 23.5% of the 3.75-mm-wide implants (p=.72). No significant differences in adverse skin reactions nor skin sensibility were observed between subgroups during and at 5 years, although, seemingly large differences between adverse skin reaction rates were found.

Conclusion

At 5-year follow-up, high implant and abutment survival rates were observed. Adverse skin reactions occurred in a minority of implants and did not significantly differ between groups. It can therefore be concluded that the 4.5-mm-wide implant, as well as the linear incision technique with soft tissue preservation procedure are safe in the long-term.

Introduction

In order to reduce postoperative complications of the bone-anchored hearing implant (BAHI), several changes in implant design and surgical technique have been made aiming to decrease complications. In 2010, the so-called wide-diameter implant was introduced. This new 4.5-mm-diameter implant has led to a larger bone-to-implant contact surface compared to the previous generation 3.75-mm-diameter implants. (1) Several clinical studies have shown superiority of this new implant design in terms of and higher implant stability quotient (ISQ) rates over the previous generation implants. (2,3) Although implant survival of the 4.5-mm-wide implant is high, a difference in survival compared with the 3.75-mm-wide implant has not been found in previous investigations. Striving to decrease adverse skin reactions and improve skin sensibility, the linear incision technique with soft tissue reduction (LIT-TR) was modified into a procedure without soft tissue reduction, so called 'soft tissue preservation'. This linear incision technique with soft tissue preservation (LIT-TP) showed more favorable results regarding skin sensibility and cosmetic outcomes. (4-6) However, no difference in adverse skin reactions was observed. Consequently, the current standard of practice regarding BAHI surgery comprise the 4.5-mm-wide implant and the LIT-TP. Although short-term outcomes seem promising, limited data is available on long-term outcomes of the 4.5-mm-wide implant and concomitant surgical techniques. (7-10)

The objections of this study are to evaluate the clinical outcomes of a 4.5-mm-wide implant and compare these to the outcomes of the previous generation 3.75-mm-wide implant, at 5-year follow-up. Furthermore, for the 4.5-mm-wide implants, clinical outcomes of the LIT-TP were compared to the LIT-TR.

Materials and methods

Study design

This study was set up as a prospective single follow-up visit 5 years after bone conduction device implantation for the patients who had completed the follow-up of two previously published prospective clinical studies conducted at our tertiary referral center. These two studies investigated and compared the 6-month and 3-year clinical outcomes of a 4.5-mm-wide implant versus the previous generation 3.75-mm-wide implant (all being inserted using LIT-TR; study A) (8,9,11) and the LIT-TP versus the LIT-TR (only containing 4.5 mm implants; study B). (6,9) In- and exclusion criteria for these two studies were identical and have been previously described. (6,7) The designs of the original studies are described below.

Study A: 4.5-mm-wide implant versus 3.75-mm-wide implant

Study A compared clinical outcomes of the 4.5-mm-wide implant with the previous generation 3.75-mm-wide implant. (7,8,10) In total, 57 patients (60 implants) were included and randomized into a test group (37 patients with 40 implants) and a control group (20 patients with 20 implants). The test group was implanted with the Wide Ponto implant (diameter 4.5 mm, length 4 mm, Oticon Medical AB, Askim, Sweden). The control group received the previous generation Ponto implant (diameter 3.75 mm, length 4 mm, Oticon Medical AB, Askim, Sweden). The same 6-mm abutment was used in all patients. All surgeries were performed between 2012 and 2014 in a one-stage procedure using the LIT-TR. (11) Follow-up visits were identical for all patients and scheduled at 7, 14, 21 and 28 days; 6 and 12 weeks; 6 months; and at 1, 2 and 3 years after implantation.

Study B: LIT-TP versus LIT-TR

Study B compared the LIT-TP with the LIT-TR for inserting BAHIs. (6,9) The test group (25 patients with 25 implants) was implanted with a Wide Ponto implant and underwent one-stage surgery in 2014 using the LIT-TP technique. (4) Abutment length (6, 9 or 12 mm) was based on skin thickness, as measured prior to local anesthesia. The control group consisted of the last 25 patients (25 implants) who already had participated in the test group of study A (described above). These patients thus underwent single-stage implantation with a Wide Ponto implant and a 6-mm abutment using the LIT-TR technique. The follow-up visits in the test group were scheduled at 7 and 21 days; 12 weeks; 6 months; and at 1, 2 and 3 years after implantation.

Patients, follow-up and outcome measures

All patients who had completed the 3-year follow-up of study A or B, and agreed to participate, were seen at a single visit 5 years after implantation. Outcomes comprised implant stability, intrasubject stability over time, implant survival, soft tissue status, skin height and revision surgery. Furthermore, skin sensibility around the abutment and subjective numbness were assessed in the patients who had participated in study B. (6) Implant stability was measured by means of the Implant Stability Quotient (ISQ) using resonance frequency analysis (RFA) and a SmartPeg 55 (Osstell AB, Göteborg, Sweden). The IPS scale was used in addition to the Holgers scale to assess soft tissue status. (12,13) A Holgers score ≥2, or an IPS-score indicating treatment, were considered an adverse skin reaction. Skin height was evaluated relative to the abutment. (6)

Data analyses

Data analyses of the 5-year follow-up data were separately conducted for patients who had originally participated in study A and for patients who had participated in study B. Analyses on implant stability and implant survival were performed on all patients who had been included in the original studies. In case of premature withdrawal from the original studies, or patients not participating in the 5-year follow-up, all collected data to the point of withdrawal were included in the analyses on implant stability and implant survival. All other outcome measures were analyzed

for the patients participating in the 5-year follow-up. In case of missing variables in the 5-year follow-up population, the last-observation-carried-forward method was used. For statistical analyses, nonparametric statistics were used. Groups were compared using the Mann–Whitney *U* test for continuous variables, the Mantel–Haenszel χ^2 test for ordered categorical variables, the Fisher's exact test for dichotomous variables, and the χ^2 test for non-ordered categorical variables. Repeated measures analyses were done for changes over time. For analyses over time, the Wilcoxon signed rank test was used for continuous variables and the Sign test was used for ordered categorical variables and dichotomous variables. To compare implant survival between groups, the Logrank survival test was used. Data analyses were executed by independent external biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden). All tests were performed using SAS v9.4 (Cary, NC), were two-tailed and conducted at a 0.05 significance level.

Ethical considerations

This 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. Informed consent was obtained in all patients.

Results

Patients

Figure 1 provides an overview of the number of participating and withdrawn patients at each time point, for both studies. In study A, a total of 48 patients (51 implants) attended the 5-year follow-up visit (84%). Since one bilaterally implanted patient had received two 4.5-mm-wide implants, the test group consisted of 33 patients (34 implants) and the control group of 17 patients (17 implants). In study B a total of 39 patients completed the 5-year follow-up (78%). Between groups, no significant differences were observed at baseline in both studies (Table 1).

Implant and abutment survival

In the total group, between the 3-year and 5-year visit, no additional implant losses had occurred. One abutment was removed in a patient with a 4.5-mm-wide implant (study A) because of cochlear implantation. Between the 4.5-mm-wide and 3.75-mm-wide implant, no significant differences in implant survival (97.4% versus 95.0%) or abutment survival (94.8% versus 95.0%) were observed. Furthermore, between patients who underwent implantation with a 4.5-mm-wide implant using either the LIT-TP or the LIT-TR, implant survival (96.0% versus 100%) and abutment survival (92.0% versus 92.0%) were comparable.

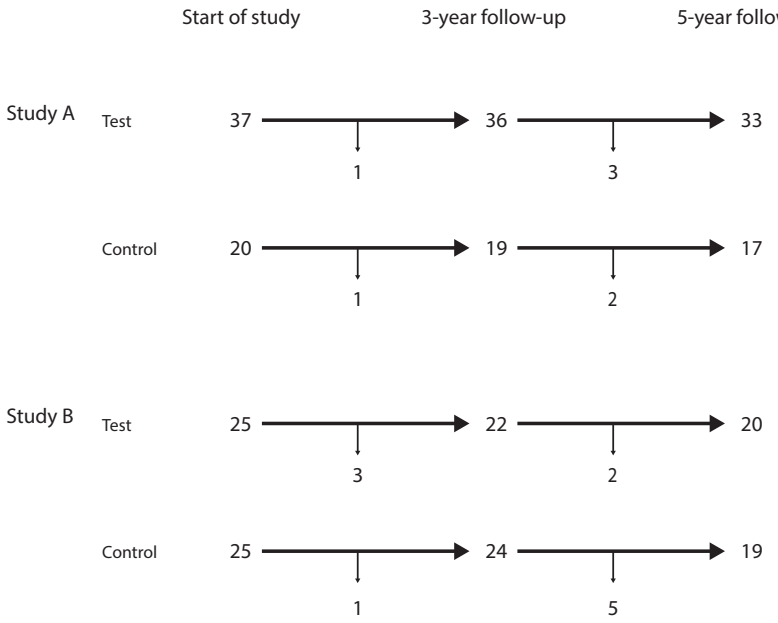


Figure 1. Flowchart demonstrating the number of patients participating in the study over time.

Reasons for withdrawal included lost-to-follow-up, deceased patient, elective removal of abutment and patient's decision to discontinue trial.

Table 1. Baseline characteristics of all patients included in study A and B.

Variable	Study A		Study B	
	4.5-mm implant Test group *n = 39*	3.75-mm implant Control group *n = 20*	LIT-TP Test group *n = 25*	LIT-TR Control group *n = 25*
Gender, n (%)				
Male	15 (38.5)	9 (45.0)	15 (60.0)	10 (40.0)
Female	24 (61.5)	11 (55.0)	10 (40.0)	15 (60.0)
Age in years, mean (SD)	53.7 (12.0)	53.0 (16.4)	51.5 (13.4)	53.9 (12.2)
Etiology, n (%)				
Acquired cond./mixed	26 (66.7)[a]	16 (80.0)	21 (84.0)	18 (72.0)
Congenital conductive	1 (2.6)[a]	1 (5.0)	1 (4.0)	0 (0.0)
Single-sided deafness	13 (33.3)[a]	3 (15.0)	3 (12.0)	7 (28.0)
Implants, n (%)				
Single implant	36 (91.2)	18 (90.0)	25 (100)	25 (100)
Two identical implants	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Two different implants	2 (5.1)	2 (10.0)	0 (0.0)	0 (0.0)

LIT-TP indicates linear incision technique with soft tissue preservation; LIT-TR, linear incision technique with soft tissue reduction

[a] *One bilaterally implanted patient had two different indications for a bone conduction device*

Implant Stability Quotient

The ISQ-low and -high are displayed in Figure 2. The inter-group differences for both the mean AUC of ISQ-low and -high were statistically significant at the 5-year follow-up (p=0.0028 and p=0.029, respectively). Between 2 and 3 years after surgery, a significant decrease in ISQ-low and -high had been observed for the 4.5-mm-wide implants. (8) At the 5-year visit, a further decrease in ISQ-low (-1.8; p=0.033) was seen in this group, compared with the 3-year visit. For the 3.75-mm-wide implants, a slight, non-significant, increase in ISQ is observed since the 2-year visit. A comparison of ISQ-values between the LIT-TP and LIT-TR resulted in a significantly higher mean AUC of ISQ-low and ISQ-high for LIT-TR, as we would expect as a result of the differences in abutment length (65.1 vs 60.8, respectively; p=0.0008 and 66.5 vs 62.2, respectively; p=0.0004). The increase in ISQ-low from surgery until the 5-year visit was significantly greater in the LIT-TP group compared to the LIT-TR group (7.85 vs 1.63, respectively; p=0.0013). For ISQ-high, a lower, but also statistically significant, increase was observed (7.60 vs 2.53, respectively; p=0.0027).

Soft tissue tolerability and complications

Figure 3 shows the Holgers-scores across visits, as well as the maximum Holgers-score per implant. Over the 5-year follow-up period, adverse Holgers scores (Holgers≥ 2) were observed in 15.2% of the 4.5-mm-wide implants and in 23.5% of the 3.75-mm-wide implants (p=0.72) for patients operated with the LIT-TR. Adverse IPS-scores were observed in 3.0% of the 4.5-mm-wide implants and in 17.6% of the 3.75-mm-wide implants (p=0.22) at the 5-year follow-up visit. At the same point, adverse Holgers scores were reported in 0.0% of the 4.5-mm-wide implants and 5.9% of the 3.75-mm-wide implants (p=0.68). In the LIT-TP versus the LIT-TR group, adverse Holgers scores were observed on at least one occasion over the 5-year period in 30.0% and in 10.5% of the implants, respectively (p=0.27). Figure 4 shows the proportion of adverse Holgers scores during the 5-year follow-up for the LIT-TP and LIT-TR group. No adverse scores were observed at the 5-year visit. Between the 3- and 5-year visit, only one patient underwent revision surgery, as described above.

At the 5-year visit, the skin height did not significantly differ between the 4.5- and 3.75-mm-wide implants, nor between the LIT-TP and LIT-TR group. For both groups, the distance between the skin and the shoulder of the abutment decreased resulting in an increased skin height (65.4% and 71.8% respectively), which never led to problems with coupling of the sound processor. In addition, no correlation between skin height and adverse Holgers scores was observed.

Skin sensibility

At the 5-year follow-up, total sensibility was comparable between the LIT-TP and LIT-TR with a median total sensibility of 100% (range 83.3 - 100) for the LIT-TP and 100% (range 75 - 100) for the LIT-TR (p=0.82), and a mean total sensibility of 96.7% (SD 5.7) for the LIT-TP and 96.3% (SD 7.1) for the LIT-TR (p=0.82). At the 5-year visit, none of the patients in either group experienced subjective numbness.

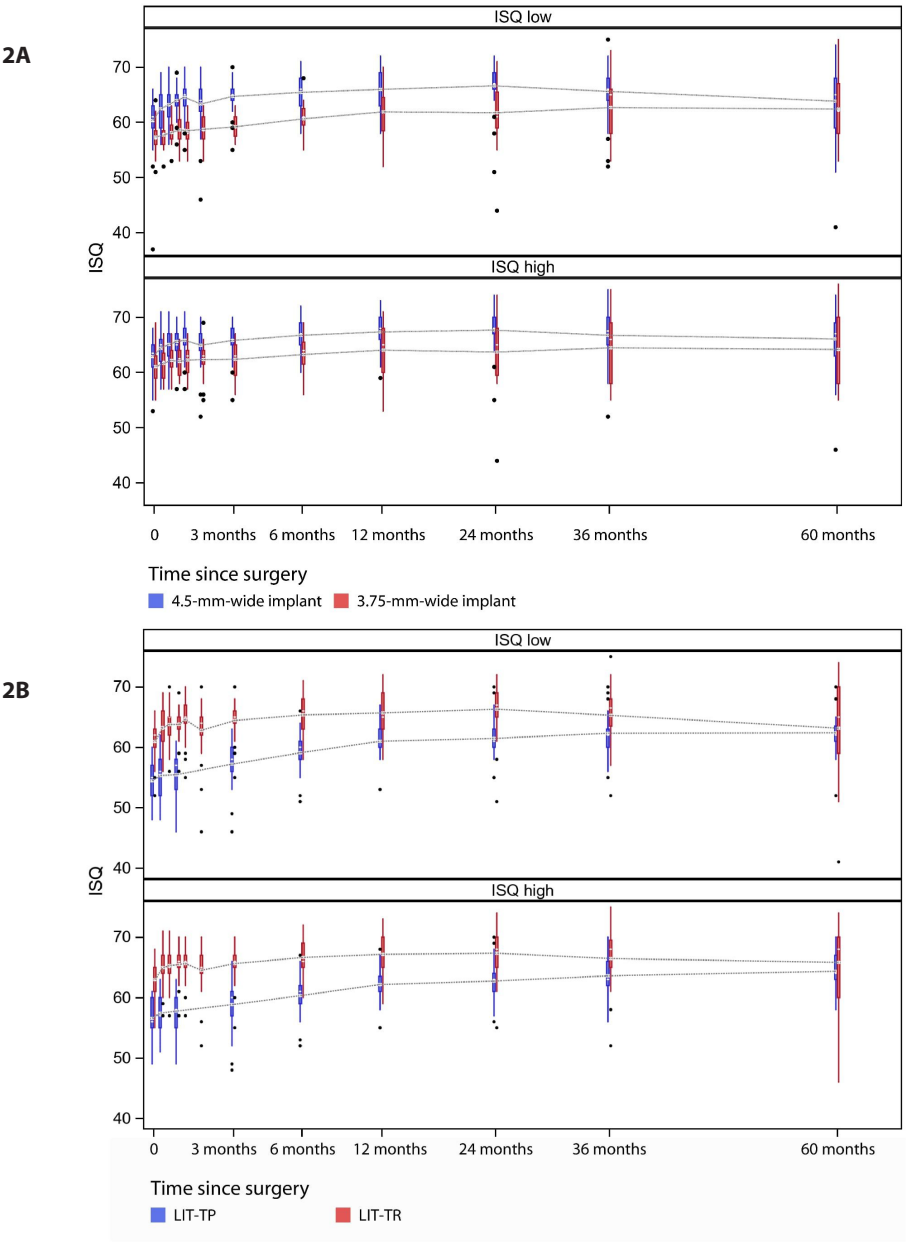


Figure 2. 2A presents Box-and-Whisker plots of ISQ-low and -high values per implant for study A, comparing a 4.5-mm-wide and 3.75-mm-wide implant. Analyses performed on 6 mm abutments exclusively. **2B** shows Box-and-Whisker plots of ISQ-low and high values per implant for study B, comparing LIT-TP and LIT-TR. Abutment size varied from 6–12 mm in the LIT-TP group, whereas only 6 mm abutments were used in the LIT-TR group.

LIT-TP indicates linear incision technique with soft tissue preservation; LIT-TR, linear incision technique with soft tissue reduction; ISQ, implant stability quotient.

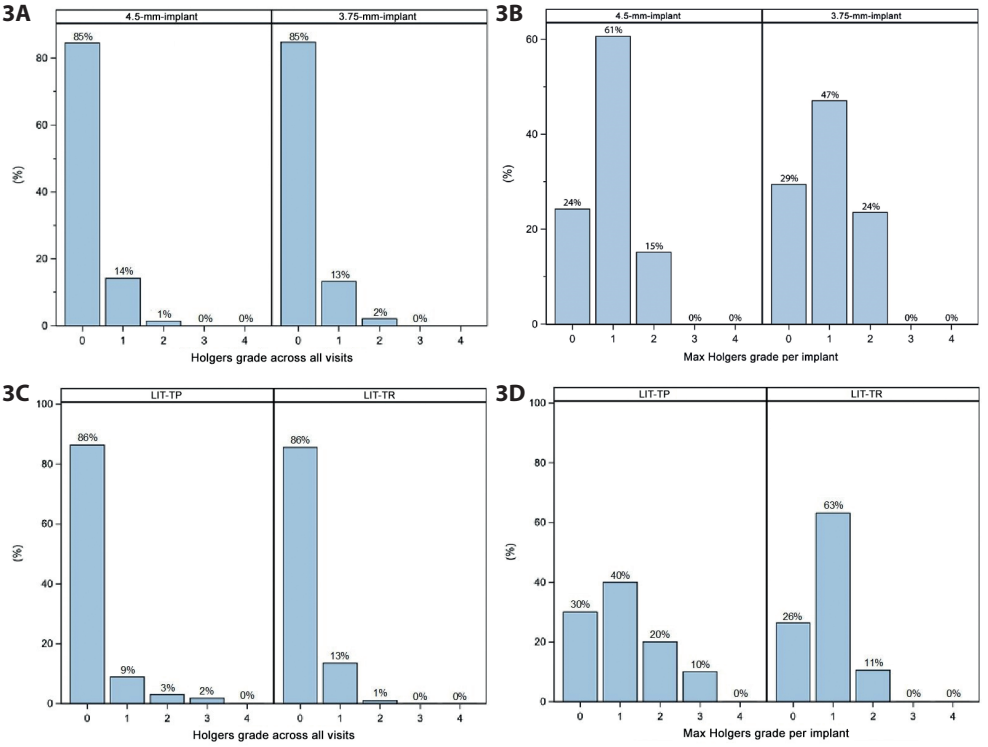


Figure 3. Holgers grade across visits (**3A**) and maximum Holgers grade **(3B**) per implant for study A, comparing a 4.5-mm-wide and 3.75-mm-wide implant. Holgers grade across visits (**3C**) and maximum Holgers grade (**3D**) per implant for study B, comparing LIT-TP and LIT-TR.

LIT-TP indicates linear incision technique with soft tissue preservation; LIT-TR linear incision technique with soft tissue reduction.

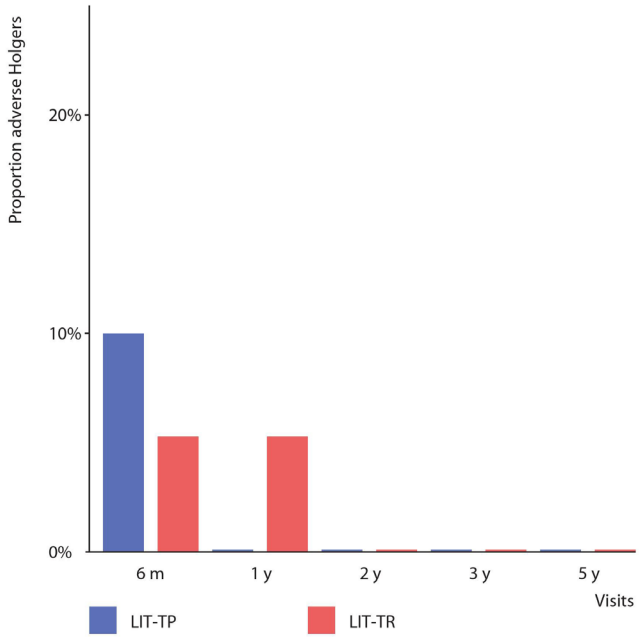


Figure 4. Proportion of adverse skin reactions measured with the Holgers score between the linear incision technique with soft tissue preservation (LIT-TP) and linear incision technique with soft tissue reduction (LIT-TR) at 6 months, 1 year, 2 years, 3 years, and 5 years follow-up.

Discussion

Main findings and clinical applicability

The current study presents the data of a 5-year single follow-up visit of patients who underwent implantation of a bone conduction device in two previously conducted clinical studies. (6,7,9,10) This provides the reader with high quality (meticulously collected) data and provides a complete overview on long-term results regarding BAHI surgery and implants.

In all four subgroups, high 5-year implant and abutment survival rates were observed. No significant differences in implant and abutment survival were observed between subgroups, but the study was also not powered for detecting such differences. The ISQ values at 5-year follow-up appear to converge for both types of implants. It can be noted that a significant correlation between ISQ values and clinical stability of percutaneous implants has not been shown up to date. In general, the ISQ data cannot be compared between the LIT-TR and LIT-TP surgical procedures because various abutment lengths were involved.

No significant differences in adverse skin reactions nor skin sensibility were observed between subgroups during and at 5 years, although, seemingly large differences between adverse skin reaction rates were found in this study. These statistically non-significant differences might be explained by limited sample sizes in this follow-up study. No difference was observed in skin height at 5 years following tissue reduction or preservation and no correlation was found with adverse soft tissue reactions. Therefore, it appears that also on the long term, the use of a wide percutaneous implant and the tissue preservation procedure leads to high stability of the percutaneous implant with a low percentage of adverse skin reactions.

As a result of the evolvement of implants and surgical techniques, the decision-making process regarding type of implant and surgical procedure has gotten more complicated over the years. (2,3, 14-16) Our results confirm the excellent survival rates of both type of implants, with higher resonance frequency properties for the 4.5-mm-wide implant. Despite this, no previous studies were able to show a better implant survival for the 4.5-mm-wide implant, mainly due to inadequate sample sizes. Further research supporting larger sample sizes should be conducted to answer this question. When comparing surgical techniques, the LIT-TP is considered to have a shorter surgery time and better cosmetic outcomes compared to the LIT-TR technique. (9) No differences in adverse skin reactions or implant survival were observed in the current study. With the current state of knowledge, we believe both implants are safe on the long-term with excellent implant survival rates. Due to the presumptive better stability the 4.5-mm-wide implant is preferred over the 3.75-mm-wide implant. Because of the shorter surgery time, less invasive character and comparable clinical outcomes, the LIT-TP is currently preferred over the LIT-TR.

Comparison with other studies

To the best of our knowledge, this is the first study to compare 5-year outcomes of both the 3.75-mm-wide and 4.5-mm-wide Ponto implant. Yet, 5-year outcomes of another 4.5-mm-wide implant type (with additionally a roughed surface) were evaluated in a multicentre study. (17) In contrast with our study, the 4.5-mm-wide implant investigated by den Besten et al., was shown to be superior in terms of adverse Holgers scores. This result could be explained by the use of two different abutment types, whereas in the current study, a difference in adverse skin reactions was not expected since similar abutments (and surgical technique and meticulous follow-up and strict aftercare) were used in both groups. Only one long-term comparative study on the LIT-TP and LIT-TR has been published. (5) In this study of Reznitsky et al., the patients were followed for 4 years (LIT-TP) or for 5 years (LIT-TR). Reznitsky et al., reported high implant survival, and adverse skin reactions were in line with our findings.

This study is one of the first studies to report IPS-scores in addition to the commonly used Holgers classification to evaluate soft tissue reactions. (8,18) The IPS provides a more comprehensive and integrated approach to skin complications compared to the Holgers classification, and also

provides a treatment advice. We would expect the greatest difference between Holgers and IPS-score, if there is any, during the period of wound healing shortly after implantation. The difference we observed at the 5-year follow-up could be explained by the characteristics of both assessment systems; with the IPS-score a more thorough and probably more conscious assessment of soft-tissue status is made compared to the Holgers-score. However, a validation of the IPS-score has yet to be conducted.

Strengths and limitations

The current study is the first study to include a long-term (5-year) follow-up after Ponto BAHI surgery with either the implant or surgical technique as variable. The data quality is considered high, as only one outcome measure was missing in one patient. A limitation is the nine patients lost to follow-up compared with the previous 3-year results of both studies, which might introduce a selection bias. All patients included in the original studies however, were included in the implant survival and ISQ analysis and handled as discussed in the methods section.

Conclusion

Independent of implant design and surgical technique, high 5-year implant and abutment survival rates were observed for patients implanted with the investigated BAHI types. Implant survival rate was 95% for the 3.75-mm-wide implant and ranged between 96% (linear incision technique with soft tissue preservation) and 100% (linear incision technique with soft tissue reduction) for the 4.5-mm-wide implant. At the 5-year follow-up visit, adverse skin reactions occurred in a minority of implants and did not significantly differ between groups. It can therefore be concluded that the 4.5-mm-wide implant, as well as the linear incision technique with soft tissue preservation procedure are safe in the long-term.

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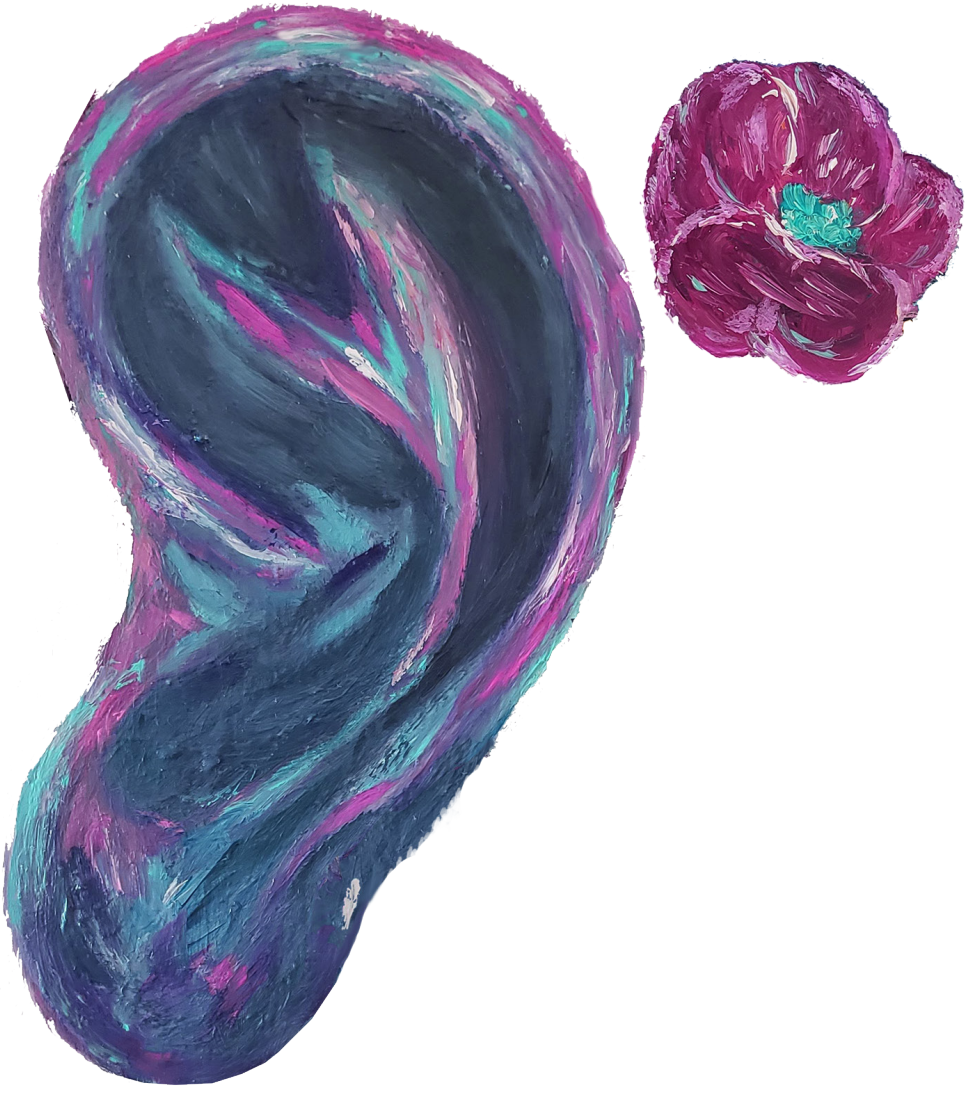

CHAPTER 3

Hearing-related quality of life in 75 patients with a percutaneous bone conduction device

Coosje J.I. Caspers
Rik C. Nelissen
Hans J.M.M. Groenewoud
Myrthe K.S. Hol

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Abstract

Objective

To evaluate long-term hearing-related quality of life (HRQoL) and sound processor use in bone conduction device (BCD) users. Furthermore, to assess differences between indications and changes in HRQoL over time.

Study design

Prospective questionnaire survey.

Setting

Tertiary referral center.

Patients

75 patients with a percutaneous BCD.

Main outcome measures

Glasgow Benefit Inventory (GBI) at 3 and 12 months postoperatively, Glasgow Health Status Inventory (GHSI) preoperatively and 6 and 36 months postoperatively, sound processor use at 6, 12 and 36 months. Changes over time were assessed and outcomes were compared between indications.

Results

After implantation, 97% of all patients reported a positive benefit on the GBI total. The GHSI total had improved with median 15 points (Interquartile range (IQR) 12). At 36 months, median sound processor use was 15 hours/day (IQR 10) and one non-user was reported. Patients with bilateral hearing loss (BHL) showed greater improvement on the GHSI total (median 18 versus 14, $p<0.0001$) and used their sound processors more frequently (median 16 versus 8 hours/day, $p<0.0001$) than patients with unilateral HL (UHL). Postoperative GHSI and GBI scores were consistent over time, in the entire patient population and for every indication. Between 6 and 36 months, sound processor use was stable over time, except for patients with single-sided deafness (SSD; median -6.4 hours/day, $p=0.009$).

Conclusion

The BCD improves HRQoL in patients with BHL, in patients with unilateral conductive/mixed hearing loss and in patients with SSD. Patients with BHL experienced a greater improvement in hearing status compared to patients with UHL. Although use decreased over time in SSD patients, sound processor use was high for every indication.

Introduction

Clinical and audiological outcomes of the percutaneous bone conduction device (BCD) are proven to be beneficial for patients with conductive/mixed hearing loss (CMHL) or single-sided deafness (SSD) who can't be rehabilitated with conventional hearing aids or surgery. (1-3) A BCD involves a surgical procedure as well as financial costs related to care and replacement of the sound processors. (3) In order to justify the use of such an implant system, cost-effectiveness studies have become increasingly important. (3-5) Unfortunately, cost-effectiveness evaluations are limited by the lack of usable data on quality of life (QoL) and sound processor usage. Generic health-related QoL questionnaires do not seem specific enough to detect changes in QoL related to the BCD. (6) Furthermore, studies on hearing-related QoL (HRQoL) either use retrospectively collected data, (7-10) or focus on short-term HRQoL in patients with a specific indication. (11,12) In these studies, HRQoL is mainly assessed by means of the Glasgow Benefit Inventory (GBI). (13) The GBI is a single-shot questionnaire which is widely used to assess the benefit of different otolaryngology interventions, (14) despite the fact that it is subject to recall bias. Status questionnaires, such as the Glasgow Health Status Inventory (GHSI), which are administered pre- and postintervention are therefore considered to be more bias-free. (13,15) Unfortunately, the GHSI is not commonly used in BCD patients. The current study evaluated prospectively collected data regarding GBI, GHSI and sound processor usage outcomes in patients who underwent BCD implantation. Specifically long-term HRQoL and sound processor use, as well as changes over time, were assessed in a general BCD population and for individual indications.

Methods

Ethical considerations

The local ethics committee approved of this study.

Study design and patient population

All data were prospectively collected in two clinical trials which were conducted at our tertiary referral center. In these studies, 80 adults underwent percutaneous BCD implantation between 2012 and 2014 with a Ponto implant® (width 3.75 mm or 4.5 mm, length 4.0mm, Oticon Medical AB, Askim, Sweden) using either the linear incision technique with soft tissue reduction or soft tissue preservation. (16-19) The 6-month HRQoL data collected in these studies have been published. (17,18) The 3-year HRQoL data of the 75 patients who completed the follow-up have not been described yet and were analyzed in the current study. The HRQoL data of these 75 patients were combined and the total study population was divided into groups based on type of hearing loss. A distinction based on etiology (acquired versus congenital) was not feasible because of the relatively small number of patients with congenital hearing loss. Firstly, the population was divided into a

group with unilateral hearing loss (UHL) and a group with bilateral hearing loss (BHL). Patients with UHL were further divided into a subgroup with CMHL and a subgroup with SSD. Because not every patient with BHL used two BCDs postoperatively, a distinction was made between patients who were postoperatively fitted with an unilateral BCD (UL fitted), and patients who were either bilateral or bimodal BCD users (BL fitted). Reasons for unilateral fitting in case of BHL were sufficient hearing with one BCD (19%), contralateral mild hearing loss (25%), unknown (25%) and contralateral profound sensorineural hearing loss (32%). Additionally, the total patient population was divided into patients with, and patients without a postoperative complication occurring within 12 months postoperatively. Postoperative complications comprised of adverse skin reactions (Holgers ≥ 2), pain, bleeding, need for abutment change, abutment removal, or revision surgery.

Questionnaires and sound processor use

Two QoL questionnaires were administered: the GHSI and the GBI.(13) Both questionnaires comprise 18 questions scored on a five-point Likert scale and result in a total score and three subscores (general, social support and physical health). The general domain (12 questions) evaluates general and psychosocial health status, whereas the social support domain (three questions) focuses on the amount of social support patients receive in relation to their impairment. The physical health score (three questions) assesses medication use and the number of visits to the general practitioner. GHSI scores range between 0 and 100 with a higher score indicating a better QoL. GBI scores range between -100 and +100 and are classified as negative (<0), no benefit (=0) or positive (>0). In this study, the GHSI was used to determine the impact of the patient' hearing impairment on HRQoL in the unaided situation before implantation. In patients using a conventional hearing aid or unilateral BCD before surgery, the GHSI was used to assess the aided situation at baseline. Additionally, the GHSI was applied to assess the aided situation at 6 and 36 months postoperatively. The GBI was used to measure change in health status after BCD implantation at 3 and 12 months postoperatively. The GBI was not assessed at 36 months because it was hypothesized that recall bias would increase with time. In addition to these questionnaires, sound processor use was determined at 6, 12, and 36 months. For patients implanted with a second BCD in the current study, sound processor use was only determined for the second device. In case of bilaterally implanted patients, the mean use of the two sound processors was assessed.

Outcome measures

Outcome measures were 12-month GBI scores, change in GHSI scores from baseline to 36 months, and 36-month sound processor use. Additionally, changes in GBI scores from 3 to 12 months, as well as changes in GHSI scores and sound processor use from 6 to 36 months were assessed. These outcomes were determined for the total study population and compared between the UHL and BHL group, the CMHL and SSD subgroup, and the UL and BL fitted subgroup. In the analyses of changes over time, outcomes were only included when data on both assessments were available. The 12-month GBI scores and sound processor use were compared between patients with and

patients without a postoperative complication within 12 months postoperatively. Correlation analysis was performed between sound processor use and outcomes on the GHSI and GBI.

Statistical analysis

Data management and analyses were partly performed by independent biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden). Non-parametric statistics were used. Outcomes were described as medians with Inter Quartile Range (IQR) and, in order to enable comparison with literature, as means with Standard Deviation (SD). For analyses of changes over time, the Wilcoxon Signed rank test was used for continuous variables and the Sign test for ordered categorical and dichotomous variables. The Mann-Whitney U test was used for comparisons between groups. Correlation analyses were performed with the Spearman correlation coefficient. Because of the observational nature of this study, corrections for multiplicity were not performed. Statistical tests were two-tailed and conducted at the 0.05 significance level. Analyses were performed by using SAS® v9.4 (Cary, NC) and SPSS statistics v25.0 (IBM Corp., Armonk, NY).

Results

Baseline characteristics are presented in table 1. All patients used a Ponto sound processor (Ponto Pro (Power) or Ponto Plus (Power); Oticon Medical AB, Askim, Sweden). The BL fitted subgroup comprised of 8 bilateral BCD users and 15 bimodal users. Out of the eight bilateral BCD users, five patients received a second BCD in the clinical trial and three patients underwent simultaneous bilateral BCD implantation. One of the bimodal users got implanted with a second BCD after 2.5 years of follow-up.

Table 1. Baseline characteristics and number of completed questionnaires for all patients and per indication group.

Cond/mixed indicates conductive/mixed hearing loss; SSD, single-sided deafness, GHSI indicates Glasgow Health Status Inventory; GBI, Glasgow Benefit Inventory; HL, hearing loss.

Variable	All patients n=75	Unilateral HL Cond/mixed n=22	Unilateral HL SSD n=14	Bilateral HL Unilateral fitted n=16	Bilateral HL Bilateral fitted n=23
Gender, n (%)					
Male	33 (44)	11 (50)	4 (29)	2 (13)	16 (70)
Female	42 (56)	11 (50)	10 (71)	14 (88)	7 (30)
Age at implantation, mean (SD)	54 (13)	52 (11)	52 (8)	56 (13)	56 (17)
Ethnicity, n (%)					
Caucasian	74 (99)	21 (96)	14 (100)	16 (100)	23 (100)
Other	1 (1)	1 (5)	0 (0)	0 (0)	(0)
Completed questionnaires, n					
Baseline - GHSI unaided	68 [a]	18	14	15	21
Baseline - GHSI aided	30	4	1	8	17
3 months - GBI	75	22	14	16	23
6 months - GHSI aided	71 [b]	19	14	16	22
12 months - GBI	75	22	14	16	23
36 months - GHSI aided	72 [c]	20	14	15	23

[a] *Two patients used their sound processor throughout the entire day and the GHSI unaided could therefore not be assessed. The GHSI unaided was missing in five other patients for unknown reasons.*

[b] *Questionnaires were missing in four patients for unknown reasons.*

[c] *Two patients were not able to complete the GHSI aided questionnaire because of sporadic sound processor use and non-use, respectively. In one patient the GHSI aided was missing for an unknown reason.*

Outcomes for the total study population

Figure 1 shows the GBI and GHSI outcomes for the total study population. For the specific GBI and GHSI scores for the total study population and per subgroup, see Table, Supplemental Digital Content 1.

GBI scores

At 12 months postoperatively, 97% of all patients had a positive GBI total score and 3% a negative total score. The GBI general score was positive in 96% and negative in 3%. The median total and general score at 12 months were 31 (IQR 27) and 42 (IQR 33), respectively. Mean scores were 32 (SD 22) and 44 (SD 26), respectively. The majority of patients had a GBI of 0 on the social support (63%) and physical health (63%) domains with median scores of 0 (IQR 17) on both domains. Mean scores were 10 (SD 21) and 8 (SD 23), respectively. Positive benefit on these domains were observed in 32% and 28%, respectively. All categorized GBI scores were similar at 3 and 12 months postoperatively.

GHSI scores

At 36 months postoperatively, the aided GHSI total and general scores significantly improved with a median of 15 (IQR 12) and 24 (IQR 7) points, respectively, when compared with the unaided scores at baseline ($p<0.0001$). The aided 36-months GHSI total and general score also improved significantly when compared with the aided scores at baseline with a median of 4 (IQR 23, $p=0.04$) and 8 points (IQR 32, $p=0.009$), respectively. No significant improvements were found for the aided GHSI social support and physical health scores at 36 months compared with the (un)aided scores before implantation. At 6 and 36 months postoperatively, all aided GHSI scores were comparable.

Sound processor use

At 36 months postoperatively, median sound processor use in hours a day was 15 (IQR 10) in the total study population. In total, 61 patients (81.3%) used their sound processor on a daily basis with a median use of 16 hours a day (IQR 4). The three patients who underwent bilateral simultaneous implantation used both their sound processors throughout the entire day. Thirteen patients (17.3%) did not use their sound processor every day and one patient (1.3%), a construction worker with unilateral conductive hearing loss, was a non-user because of practical reasons. The 13 non-daily users were comprised of ten patients with UHL (six with SSD), two with bimodal fitting and one unilateral BCD user with BHL. Median use in this group was two days per week. Sound processor use did not change significantly between 6 and 36 months.

Correlation analyses

Sound processor use at 36 months was positively correlated with the postoperative change on the GHSI total and general score (change from baseline unaided to 36 months aided). In these cases, weak, but statistically significant, correlations were found ($r=0.31$, $p=0.01$ and $r=0.33$, $p=0.008$, respectively). No correlations were observed between sound processor use and the GHSI social support and physical health scores. The GBI scores at 12 months did not correlate with sound processor use at 12 months (for GBI total $p=0.14$). Postoperative complications did not influence the 12-month GBI scores and sound processor use.

Outcomes compared between indication (sub)groups

Figure 2 presents the GBI and GHSI total scores across visits for the different indications. A comparison of baseline GHSI scores between the indication (sub)groups was only performed for the unaided scores, because of the limited number of patients completing the aided GHSI at baseline (table 1). Figure 3 demonstrates sound processor use per indication group.

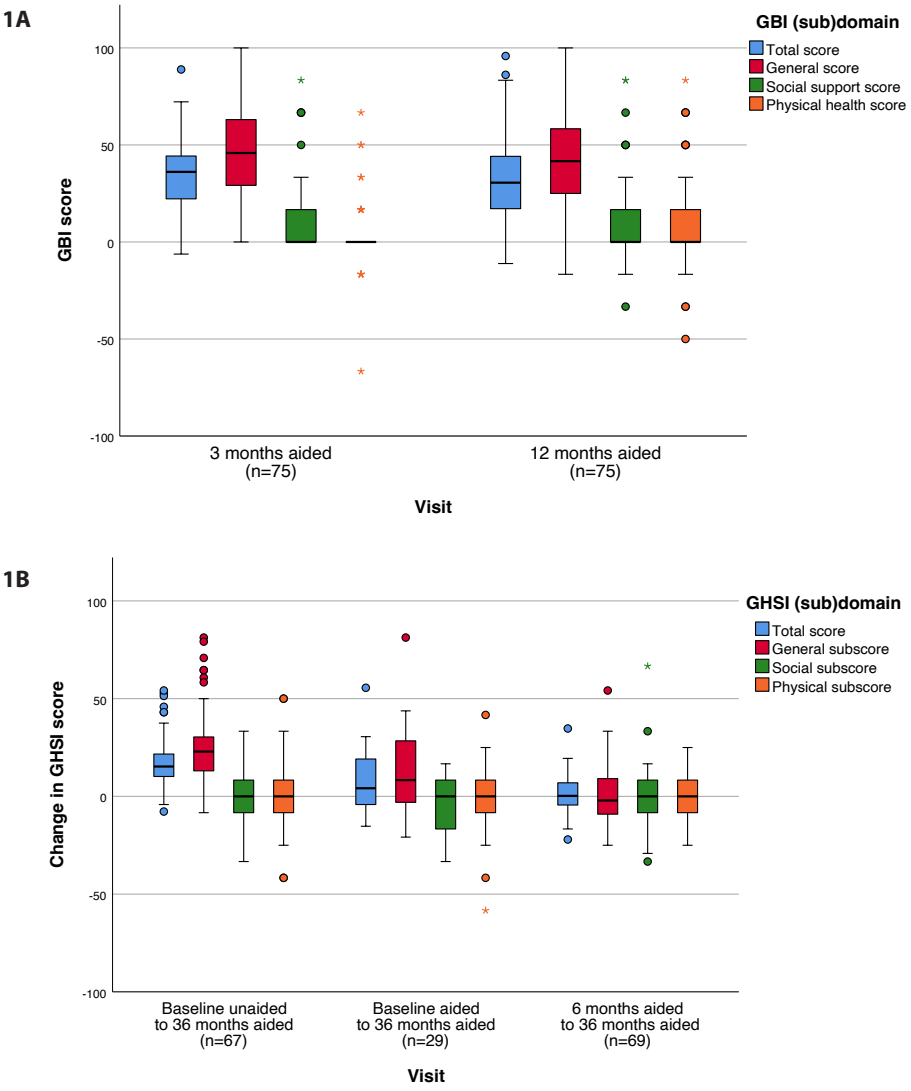
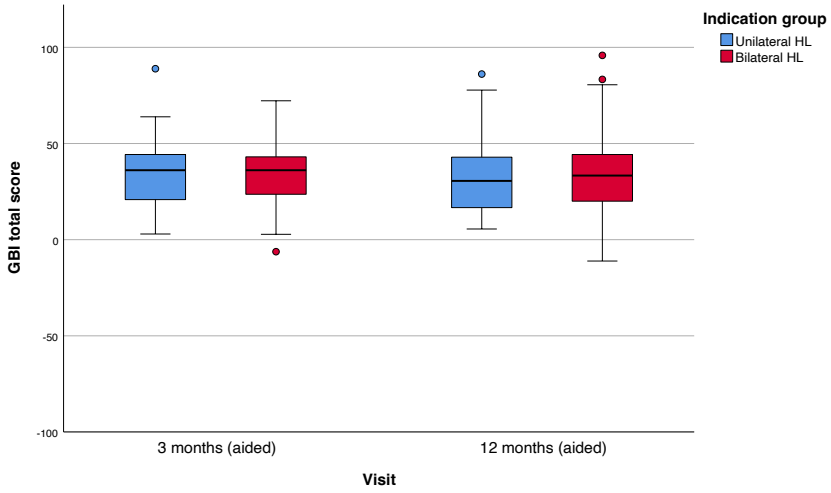


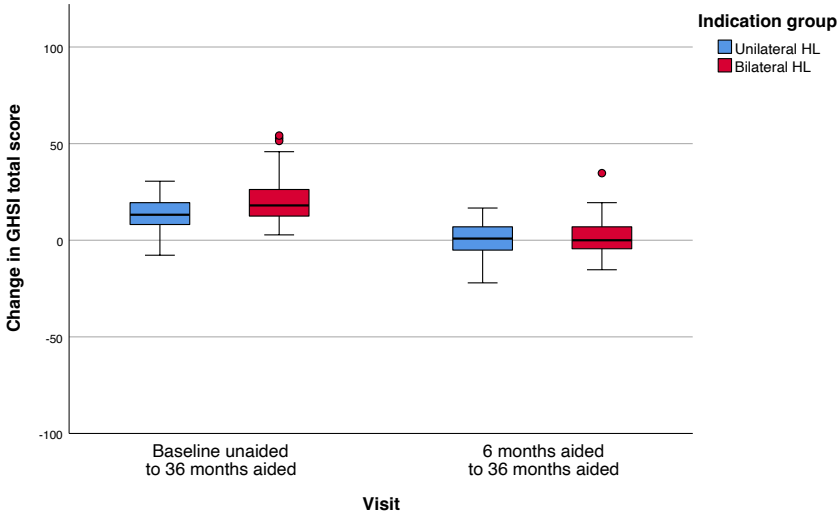
Figure 1. Boxplot of the GBI (sub)scores (**1A**) and changes in GHSI (sub)scores (**1B**) across visits for the total study population.

The median is marked by a horizontal line. The boxplots represent the interquartile range, whiskers represent the range with the exception of outliers, the dots represent outliers, and the asterisks represent extreme outliers. GBI indicates Glasgow Benefit Inventory; GHSI, Glasgow Health Status Inventory.

2A


Indication group
Unilateral HL
Bilateral HL
GBI total score
100
50
0
-50
-100
3 months (aided)
12 months (aided)
Visit

2B


Indication group
Unilateral HL
Bilateral HL
Change in GHSI total score
100
50
0
-50
-100
Baseline unaided
to 36 months aided
6 months aided
to 36 months aided
Visit

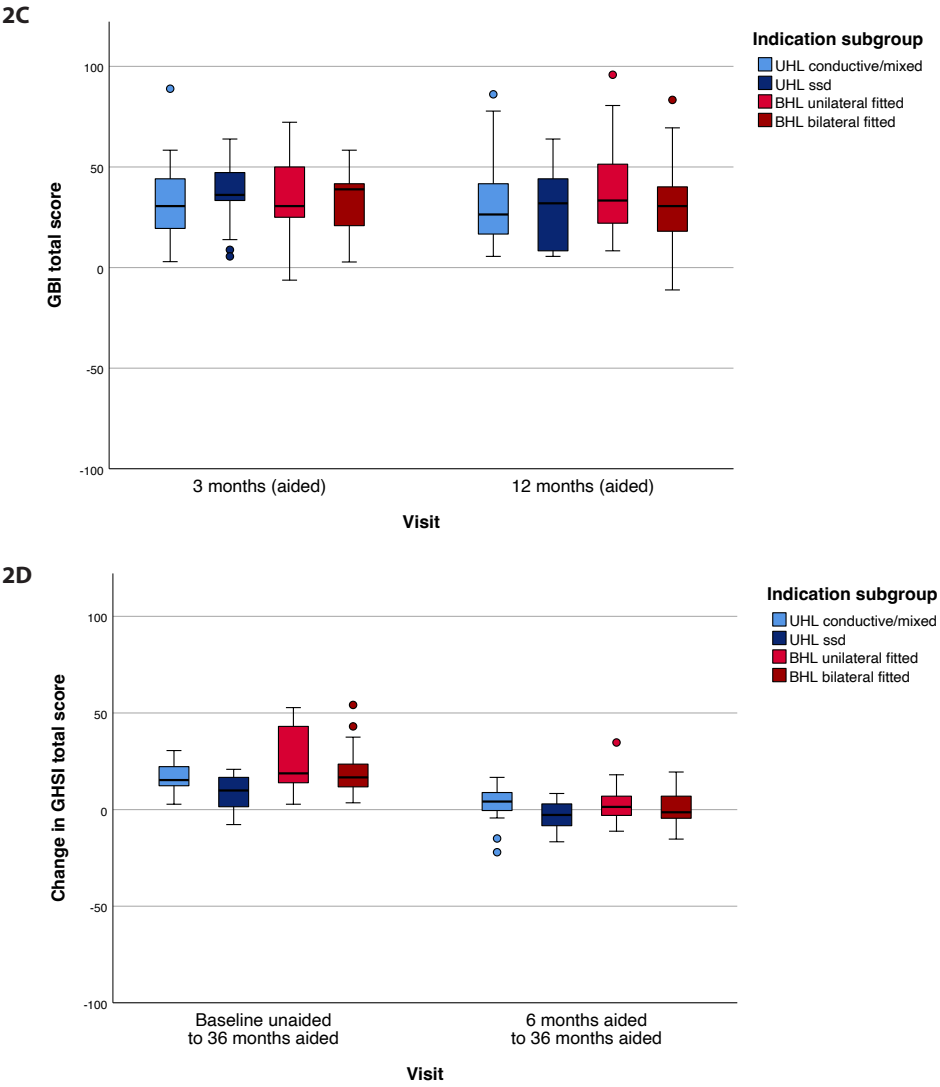


Figure 2. Boxplots presenting the GBI total score and change in GHSI total score by indication groups (figure **2A** and **2B** respectively) and by indication subgroups (figure **2C** and **2D** respectively.)

The median is marked by a horizontal line. The boxplots represent the interquartile range, the whiskers represent the range with the exception of outliers, the dots represent outliers, and the asterisks represent extreme outliers. GBI indicates Glasgow Benefit Inventory; GHSI, Glasgow Health Status Inventory.

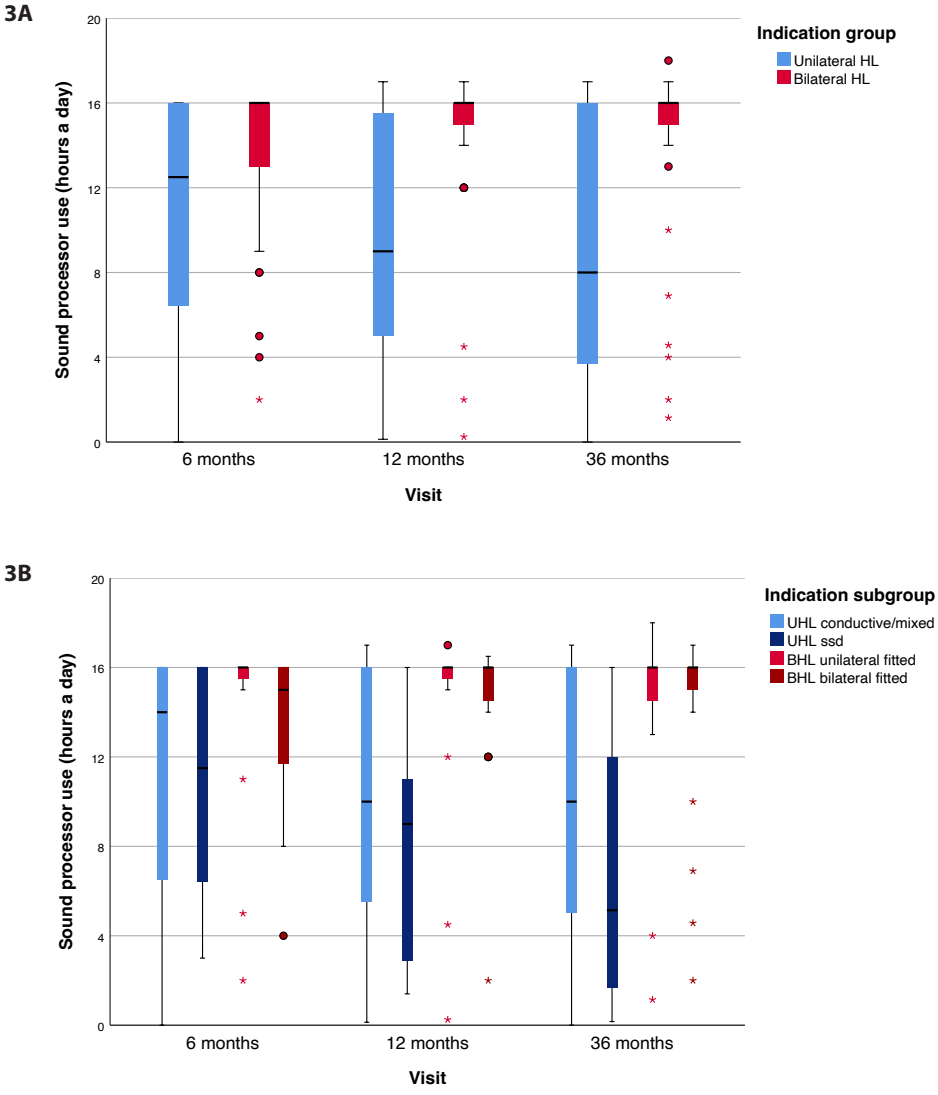


Figure 3. Boxplots presenting sound processor use in hours a day compared between indication groups (**3A**) and indication subgroups (**3B**).

The median is marked by a horizontal line. The boxplots represent the interquartile range, the whiskers represent the range with the exception of outliers, the dots represent outliers, and the asterisks represent extreme outliers.

Unilateral versus bilateral hearing loss

The categorized GBI scores at 3 and 12 months, as well as changes in GBI scores over time, were comparable for patients with UHL and BHL. Before implantation however, patients with UHL had a significantly higher unaided GHSI total score, as well as better general and physical health scores, compared to patients with BHL. The social support score at baseline was however higher for the patients with BHL. The GHSI total and general score at 6 and 36 months had significantly improved for both groups compared with the unaided baseline scores, with a greater improvement for the BHL group. Median change in total score from baseline to 36 months was +14 (IQR 12) in case of UHL and +18 (IQR 13) in case of BHL ($p<0.0001$). In both groups, the postoperative aided GHSI social support- and physical health score were similar to the unaided scores at baseline.

At all time-points of assessment (6, 12 and 36 months), patients with BHL used their sound processors (either first or second BCD) more often than patients with UHL, with a median difference of 8 hours a day at 36 months ($p<0.001$). Between 6 and 36 months, sound processor use was consistent in the BHL group, but significantly deteriorated over time in the UHL group with a median difference of 4.5 hours a day ($p=0.019$).

CMHL versus SSD

Within the UHL group, the categorized GBI total score, as well as the general and social support scores were comparable between subgroups at 3 and 12 months. The physical health score was significantly lower for the SSD patients. A positive benefit on the physical health domain was reported in nine patients (41%) with CMHL and in only one patient (7%) with SSD ($p=0.027$). GBI scores were consistent over time except for a slightly increased physical health score in the CMHL subgroup at 12 months.

At baseline, similar unaided GHSI scores were observed for the CMHL and SSD subgroups. At 6 and 36 months, the total and general score had improved in both subgroups, compared with baseline unaided scores. However, at 36 months a greater improvement in these scores was found for patients with CMHL ($p=0.021$ and $p=0.026$).

Sound processor use at both 6 and 36 months was comparable between groups. However, in the SSD subgroup, sound processor use decreased over time between 6 and 36 months with a median of 6.4 hours a day ($p=0.009$). At 36 months, median use in the SSD subgroup was 5.1 hours a day (IQR 11) and 57% used their sound processors on a daily base. For the CMHL subgroup, sound processor use did not change significantly over time ($p=0.53$).

Unilateral versus bilateral fitting

For patients with bilateral HL, categorized GBI scores a and changes in GBI over time were all comparable between the UL and BL fitted subgroups at both time points. Unaided GHSI scores

at baseline were comparable between patients with UL and BL fitting, except for a slightly worse physical health score in the BL fitted subgroup (mean difference -13, p=0.049). Postoperative GHSI scores at 6 and 36 months had significantly improved for both groups compared to the unaided baseline scores, with a similar improvement in the total and general score. The social support and physical health score remained similar to baseline in both UL and BL fitted patients. In both groups, sound processor use was consistent over time. Similar and high usage rates were observed at 6, 12 and 36 months postoperatively.

Discussion

Key findings and interpretation

The current study evaluated hearing-related quality of life (HRQoL) in 75 patients with a percutaneous bone conduction device (BCD), among and across separate indications. After BCD implantation, the majority of patients reported a positive benefit on the Glasgow Benefit Inventory (GBI) total (97%) and general (96%) domain and the Glasgow Health Status Inventory (GHSI) total and general score had significantly improved. In every indication (sub)group, postoperative improvement in HRQoL was observed. Interestingly, postoperative GBI and GHSI scores were consistent over time, in the entire patient population and in every indication group. During follow-up, high sound processor usage rates were reported among and across individual indications with only one non-user at 36 months. Except in patients with SSD, sound processor use was stable over time. The current findings underline that BCD implantation results in an improved HRQoL in patients with bilateral conductive/mixed hearing loss (CMHL) and suggest an improved HRQoL in patients with unilateral CMHL and in patients with SSD. The consistency in HRQoL over time, as measured with the GBI and GHSI, might imply that a one-time assessment of the GBI (postoperatively) and GHSI (pre- and postoperatively) is sufficient. In addition, the postoperative time point of questionnaire assessment seems to be of minor importance. We might therefore conclude that GHSI- and GBI outcomes can be compared across studies, independent of time of assessment. On the other hand, the current study only evaluated 12-month GBI and 36-month GHSI outcomes. HRQoL outcomes might change over time in case of even longer follow-ups. Especially since previous studies observed a tendency towards decreasing benefit and sound processor use in patients with SSD, at three to five years follow-up. (20-22) A future study investigating the long-term (>10 years) stability of HRQoL in different indication groups, using modern sound processor technology, would be of interest.

Differences between indications

GBI scores were comparable between indication (sub)groups. This might indicate that the level of benefit achieved with a BCD is independent of indication. More probable explanations include insufficient sensitivity of the GBI, small sample size per group, and heterogeneity in

patient characteristics. According to the GHSI outcomes, patients with bilateral hearing loss (BHL) experienced a greater improvement in hearing status after BCD implantation (either first or second BCD) than patients with unilateral hearing loss (UHL). The postoperative change in GHSI total and general scores at 36 months had a weak, but significant positive correlation with sound processor use indicating that satisfied users use their sound processors more frequently. Not surprisingly, patients with BHL used their sound processor more frequently than patients with UHL. These findings are in line with previous studies in which a higher subjective benefit and sound processor usage rate were found for patients with BHL. (7,10) In the current study, sound processor use decreased over time in patients with UHL. This decrease can most probably be attributed to the patients with SSD, as use deteriorated with time in this subgroup. This finding suggests, in line with literature, that sound processor use deteriorates over time in SSD patients. Despite the deteriorating use, the majority of SSD patients still seemed to benefit from a BCD, since 57% of them used the BCD on a daily base at three years after implantation. Additionally, GHSI scores remained stable over time in this subgroup indicating that these patients still experience benefit from the BCD at three years postoperatively. When counseling a patient with SSD applying for a BCD, it is however important to discuss the variability in usage times among patients and the deterioration in use.

Comparison with literature

In line with our findings, Meghji et al. found significantly improved GHSI total and general scores after surgery. (23) Interestingly, in their study, the physical health score also increased postoperatively. In the current study, both the categorized GBI and mean GBI scores were reported. According to Hendry et al., categorized GBI scores enable better comparisons between interventions.(14) Unfortunately, most studies report mean GBI scores only. Studies evaluating HRQoL in a BCD population with mixed indications reported mean total GBI scores ranging between 31 and 38. (10,24,25) In these studies, the highest mean scores were found on the general domain, followed by the social support and physical health scores. GBI results for our study population were similar, with a mean total score of 32 and the highest mean score being observed in the general domain. Although the mean social support and physical health scores were 10 and 8 respectively, the majority of our patients did not experience a positive benefit in these domains. This finding seems plausible since these domains are related to more generic QoL and do not assess health items which might be influenced by BCD implantation. The number of visits to the ENT-department or number of ear infections are for instance not included in the GBI. In the current study, a positive total GBI benefit was observed in 97%. De Wolf et al., assessed the GBI in older patients with a conventional indication and found a positive benefit in 84%. (9) The higher benefit percentage in the current study might be explained by advancements in sound processor technology or lower age. HRQoL studies on cholesteatoma surgery and stapes surgery observed positive benefit on the GBI total in 82% and 85% of the patients respectively. (26,27) It must however be noted that in the study on cholesteatoma surgery, ossicular reconstruction was not performed in 12%. (27) In general, GBI total benefit scores after BCD implantation appear to be at least comparable to those

after reconstructive middle ear surgery. In terms of HRQoL, hearing rehabilitation with a BCD thus seems to be a good alternative to surgical restoration in indicated patients.

Sound processor use in our study population was in line with literature, with a mean use of 11 hours a day for the total study population and 81% daily users. Lekue et al., evaluated a population with mixed indications as well and observed a mean use of 11 hours a day and daily use in 72% of the patients. (10)

Strengths and limitations

This study provides new insights into long-term HRQoL, the consistency of HRQoL over time and differences in HRQoL between indication groups. The use of prospectively collected data and the relatively large sample size are the major strengths of this study. However, dividing the study population into different indication groups, resulted in small subgroups with heterogenous characteristics. For instance, the UL fitted subgroup comprised patients with bilateral conductive hearing loss, as well as patients with conductive hearing loss on the side of implantation and a contralateral profound sensorineural hearing loss. Furthermore, the BL fitted subgroup consisted of both bilateral and bimodal BCD users. In these patients, sound processor use was only assessed for the BCD that was implanted during the clinical trial. Despite the heterogeneity within subgroups, plausible differences in HRQoL between groups were found in this study.

Conclusion

The bone conduction device improves hearing-related quality of life in patients with both unilateral and bilateral conductive/mixed hearing loss (CMHL), and in patients with single-sided deafness. Patients with bilateral hearing loss experienced a greater improvement in hearing status compared to patients with unilateral hearing loss. At 36 months, high sound processor usage rates were observed in every indication group. However, sound processor use decreased over time in patients with single-sided deafness. Outcomes on the GBI and GHSI questionnaire were stable over time across and among separate indications.

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Supplemental material

Supplemental digital content 1, Table. Glasgow Health Status Inventory and Glasgow Benefit Scale total and general scores at all time points, for the study population as a whole and for each subgroup.

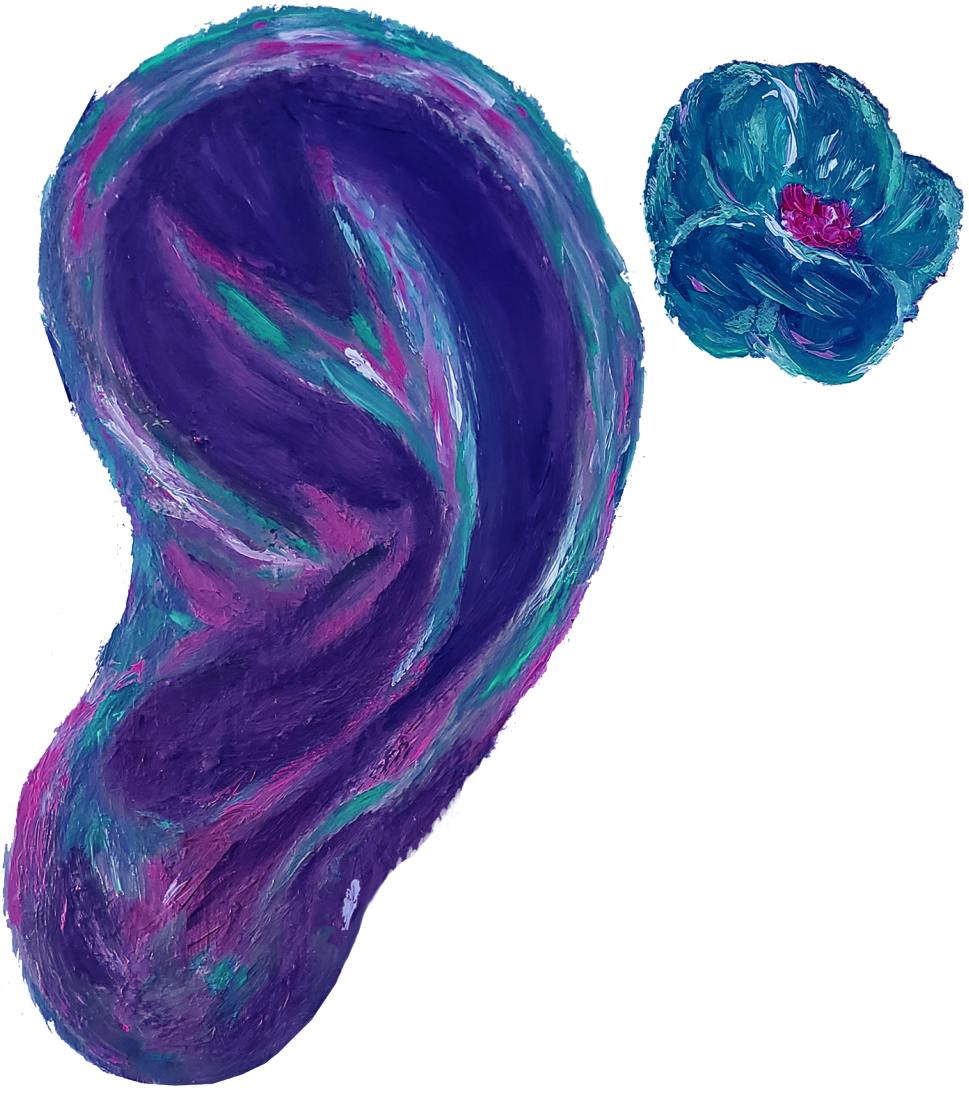
HL indicates hearing loss; SSD, single-sided deafness.

Variable	All patients Mean (SD) Median (min; max) n	Unilateral HL conductive/mixed Mean (SD) Median (min;max) n	Unilateral HL SSD Mean (SD) Median (min; max) n	Bilateral HL Unilateral fitting Mean (SD) Median (min; max) n	Bilateral HL Bilateral fitting Mean (SD) Median (min; max) n
Glasgow Health Status Inventory					
Baseline – unaided (n)					
Total score	50 (13) 52 (26; 75) 68	56 (12) 57 (35; 74) 18	55 (11) 56 (32; 75) 14	48 (15) 53 (26; 69) 15	42 (10) 40 (26; 65) 21
General score	40 (16) 42 (4; 69) 68	49 (12) 51 (30; 67) 18	47 (13) 48 (17; 69) 14	37 (17) 41 (4; 65) 15	31 (15) 30 (8; 65) 21
Baseline – aided					
Total score	55 (18) 51 (19; 86) 30	64 (26) 72 (28; 86) 4	46 1	62 (22) 66 (19; 85) 8	49 (12) 49 (22; 67) 17
General score	48 (21) 46 (8; 88) 30	60 (23) 65 (27; 81) 4	38 1	59 (27) 61 (8; 88) 8	41 (15) 42 (15; 69) 17
6 months – aided					
Total score	66 (12) 68 (43; 90) 71	69 (9) 69 (47; 89) 19	66 (11) 66 (51; 88) 14	68 (12) 68 (47; 90) 16	61 (13) 59 (44; 85) 22

General score	65 (15) 65 (33; 94) 74	71 (12) 71 (48; 94) 21	63 (13) 61 (46; 85) 14	68 (15) 68 (33; 90) 16	58 (16) 58 (35; 88)) 23
36 months – aided		2			
Total score	66 (15) 68 (33; 92) 72	71 (12) 69 (47; 92) 20	64 (12) 60 (42; 82) 14	73 (13) 78 (49; 88) 15	60 (16) 53 (33; 90) 23
General score	65 (19) 64 (15; 96) 73	72 (14) 73 (45; 96) 21	60 (18) 59 (29; 93) 14	73 (19) 83 (39; 94) 15	57 (21) 54 (15; 96) 23
Glasgow Benefit Inventory					
3 months - aided					
Total score	34 (18) 36 (-6; 89) 75	33 (19) 31 (3; 89) 22	36 (17) 36 (6; 64) 14	35 (20) 31 (-6; 72) 16	33 (16) 39 (3; 58) 23
General score	47 (23) 46 (0; 100) 75	44 (25) 46 (0; 100) 22	49 (22) 54 (8; 82) 14	50 (24) 42 (10; 96) 16	47 (23) 50 (4; 88) 23
12 months - aided					
Total score	32 (22) 31 (-11; 96) 75	33 (22) 26 (6; 86) 22	29 (18) 32 (6; 64) 14	36 (20) 33 (8; 81) 16	30 (22) 31 (-11; 83) 23
General score	44 (26) 42 (-17; 100) 75	42 (26) 33 (0; 96) 22	42 (23) 48 (13; 88) 14	50 (26) 44 (21; 100) 16	41 (28) 50 (-17; 100) 23

PART II

Investigating a minimally invasive surgical technique



CHAPTER 4

Six-month clinical outcomes for bone-anchored hearing implants: comparison between minimally invasive Ponto surgery and the linear incision technique with tissue preservation

Coosje J.I. Caspers
Ivo J. Kruyt
Emmanuel A.M. Mylanus
Myrthe K.S. Hol

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Abstract

Objectives

To investigate and compare the clinical outcomes of minimally invasive Ponto surgery (MIPS) to the linear incision technique with soft tissue preservation (LIT-TP) for percutaneous bone-anchored hearing implants (BAHI).

Study design

Prospective cohort study with a historical control group.

Setting

Tertiary referral center.

Patients

25 patients were prospectively included in the test group. The control group consisted of 25 patients who previously participated in another clinical trial and already underwent BAHI surgery.

Intervention

All patients were implanted with a 4.5-mm-wide implant, using MIPS in the test group and the LIT-TP in the control group. Follow-up visits were scheduled 7 days, 21 days (sound processor fitting), 12 weeks and 6 months after surgery.

Main outcome measures

The primary outcome measure was skin sensibility around the abutment six months after surgery. Secondary outcomes were subjective numbness, surgery time, wound healing, adverse soft tissue reactions, cosmetic outcomes, Implant Stability Quotient (ISQ), implant survival, and sound processor use.

Results

Skin sensibility, adverse soft tissue reactions and sound processor use were comparable between groups. The test group had a shorter surgery time and better cosmetic outcomes. More skin dehiscences and a statistically non-significant higher implant loss rate (12% versus 0%, p=0.079) were observed in the test group.

Conclusion

MIPS is comparable to the LIT-TP regarding skin sensibility at six months and soft tissue tolerability. With MIPS, surgery time is further reduced and better cosmetic outcomes are reported. More research into MIPS, exact drill protocol, used instruments and associated implant loss is warranted.

Introduction

Because of its favorable outcomes, the linear incision technique with soft tissue preservation (LIT-TP) is nowadays the most regularly used procedure to insert bone-anchored hearing implants (BAHIs). Nevertheless, in an attempt to further reduce soft tissue damage and improve clinical outcomes, several punch-only techniques were developed in recent years. (1-4) When using such a technique, no sutures are needed and, therefore, no scar is visible after surgery. These procedures are also thought to result in decreased surgery times, faster wound healing, less postoperative discomfort, better cosmetic appearance and less numbness. (1,4) A punch-only technique implies working through a keyhole. The downside of a small surgical area is the limited intraoperative visibility resulting in more difficulty to insert the implant perpendicular to the bone, and to control bleeding and prevent damage to the subcutaneous tissue. Another challenge is to provide adequate cooling to the bone while drilling. To overcome these challenges, minimally invasive Ponto surgery (MIPS) was developed. This is a standardized punch-only procedure with standardized equipment providing both irrigation of the bone and (by means of a cannula) protection of the surrounding soft tissue while drilling. (5,6) Short-term outcomes of MIPS showed favorable results regarding numbness, wound healing, cosmetic appearance and soft tissue tolerability. (6-10) However, only two studies compared MIPS with the currently most advocated technique, the LIT-TP (9,10), whereby Giustino *et al*. (9) performed a retrospective study with a small sample size and the study of Calon *et al*. (10) had a postoperative follow-up of only 12 weeks. Therefore, additional clinical evaluations are warranted with more patients involved and longer follow-up.

To assess the added value of MIPS, the current prospective study compared the six-month clinical outcomes of MIPS with the LIT-TP whereby clinical conditions were kept identical in both groups.

Materials and Methods

Patients in the test group were scheduled for MIPS. The control group consisted of patients who participated in another clinical trial (11,12) and had already undergone BAHI surgery using the LIT-TP. The same inclusion and exclusion criteria applied for test and control group: patients aged 18 years or older indicated for a percutaneous BAHI were included. The exclusion criteria consisted of 1) reimplantation surgery, 2) skin thickness >12mm, 3) diseases or treatments known to have an effect on skull bone quality, e.g. osteoporosis, radiotherapy, or unstable blood glucose levels caused by diabetes mellitus, 4) a medical history of psychiatric disease or mental disability, 5) inability to participate in follow-up, 6) an intra-operative switch to an alternative surgical technique. Patients who had already been included in the control group and were afterwards eligible for a second percutaneous BAHI, were not included in the test group.

Surgical procedures and follow-up

All surgical procedures were carried out by one of the two experienced ENT-surgeons (EM and MH), trained in performing MIPS prior to the start of the trial. In both groups, a Wide Ponto implant® (diameter 4.5 mm, length 4.0 mm, Oticon Medical AB, Askim, Sweden) with abutment (6, 9, or 12mm) was placed in a one-stage surgery. Abutment length was determined by assessing skin thickness prior to infiltration of local anesthetics.

MIPS was conducted in the test group, whereby a biopsy punch is used to create a 5-mm circular incision (figure 1). Following removal of periosteum with a raspatorium, a cannula is inserted. Stepwise drilling is performed through this cannula using saline for adequate cooling. According to the manufacturer's instruction for MIPS, drilling should be performed in three steps: 1) drilling of a 3-mm hole using the canula guide drill with spacer, 2) deepening the hole to 4 mm using the same drill without spacer, and 3) widening the 4-mm hole using the cannula widening drill. At our center, however, BAHIs are inserted in adults with two-step drilling, i.e. without the use of the guide drill with spacer. Because of the excellent results of this two-step drilling protocol at our center (6,13), two-step drilling was performed in the current study. After stepwise drilling, with adequate cooling, the cannula is removed and the implant (with selected abutment) is inserted in the bone, in this study using constant irrigation. During implant insertion, the number of rotations is counted using an insertion indicator to determine whether full insertion is achieved. In case of incomplete insertion, manual tightening is additionally performed.

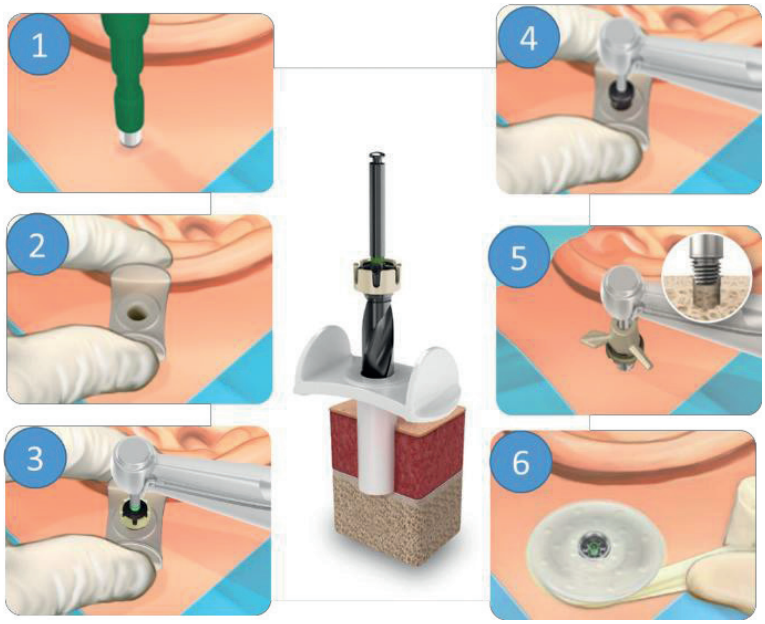

Figure 1. MIPS procedure: 1) 5-mm biopsy punch is used to create a circular incision. 2) Cannula is inserted. 3 and 4) Stepwise drilling is performed. 5) Cannula is removed and the implant is inserted. 6) Healing cap with dressing is placed. *Image provided by Oticon Medical ™. Reprinted with permission.*

In the control group, BAHI insertion was performed using the LIT-TP as described by Hultcrantz. (14) Hereby, a linear incision is made down to the skull bone, followed by complete periosteum removal. Two-step drilling is performed, and the implant-abutment complex is inserted. After closing the skin over the abutment using sutures, a 5-mm punch hole is made for the abutment to penetrate the skin. This punch is either placed in, or posterior to the line of incision. In both groups, a healing cap and dressing with Terra-Cortril® (antibiotic ointment containing hydrocortisone, oxytetracycline and polymyxin-B) was placed onto the abutment at the end of surgery. Seven days after surgery, the healing cap was removed, and all patients were instructed to apply Terra-Cortril® on the peri-abutment skin twice daily for two weeks. Demographic and patient characteristics were assessed preoperatively. Follow-up visits were identical for both groups and were scheduled at 7 days, 21 days (sound processor fitting), 12 weeks, and 6 months postoperatively.

Outcome measures

The primary outcome of this study was skin sensibility around the abutment six months after surgery. This primary outcome was based on the primary outcome of the study in which the control group patients had participated. (11,12) In the present study, it was hypothesized that MIPS would improve skin sensibility even further compared with the LIT-TP. In MIPS, no linear incision is made, leaving the nerves, and thereby skin sensibility, around the abutment intact. By using a broken wooden cotton swab, gnostic (cotton tip) and vital (sharp end) sensibility were both assessed at six standardized locations (12) and reported as a percentage of correct answers.

As a secondary outcome, subjective numbness was rated by the patient on a ten-step scale with 0 indicating no numbness and 10 indicating complete numbness. The diameter of the numb area was also reported. Additional secondary outcomes which were compared between groups were surgery time, healing time, need for revision surgery, soft tissue reactions, cosmetic outcomes, implant stability and survival, and sound processor use. Adverse events, unplanned visits and postoperative complications, such as hematoma and skin dehiscence were also reported. Surgery time was determined in minutes and measured from punch to complete implant insertion in the test group, and from incision to wound closure in the control group. Skin status was determined by the Holgers classification (15) and adverse soft tissue reactions were defined as Holgers≥2. The Patient and Observer Scar Assessment (POSAS) v2.0 (16) was used to assess cosmetic outcomes, whereby both patient and observer rated six scar characteristics on a ten-step scale. A total score, ranging between 6 and 60, is calculated, with a higher score indicating worse cosmetic outcome. Additionally, an overall opinion is scored by both patient and observer. Implant stability was evaluated by assessing the Implant Stability Quotient (ISQ) (11,12,17), directly after implant installment and during every follow-up visit. ISQ was determined by resonance frequency analysis, using the Osstell® ISQ device (Osstell AB, Göteborg, Sweden) and a SmartPeg (type 55) on the abutment. The highest and lowest score observed during perpendicular measurements were reported.

Sample size

At study initiation, no data were available for statistical sample size calculation regarding skin sensibility in relation to BAHI surgery. Sample size has instead been based on the investigators' experience, the sample size of the previous performed trial (11,12) and on logistical feasibility. It was decided to include a total of 50 patients, consisting of 25 patients per group.

Statistical analysis

Data analysis was conducted by independent external biostatisticians (Statistika Konsultgruppen, Göteborg, Sweden). Non-parametric tests were used to perform statistical analysis. Outcomes were compared between groups using the Mann-Whitney U-test for continuous variables, the Mantel Haenzsel chi-square test for ordered categorical variables, Fisher's exact test for dichotomous variables, and a Chi-square test for non-ordered categorical variables. Changes over time were analyzed with the Wilcoxon Signed rank test in case of continuous variables, and with the Sign test in case of categorical and dichotomous variables. Correlation analysis was performed using the Spearman correlation coefficient. In case of premature withdrawal, all collected data to the point of withdrawal were included in the analysis. All statistical tests were carried out using SAS® v9.4 (Cary, NC). A Confidence interval (CI) of 95% was adopted, and statistical significance was defined as a p-value < 0.05.

Ethical considerations

This study was approved by the local ethical committee and was performed according to ISO14155:2011, the Good Clinical Practice guideline and the ethical principles stated by the Declaration of Helsinki. (18) Upon inclusion, written informed consent was obtained from all patients.

Results

Demographics and follow-up

A total of 50 patients were included: 25 patients in the control group between February and August 2014 (12) and 25 patients in the test group between June and December 2017. Except for an older age in the test group (mean difference 9.0 years, p=0.019), no significant differences between groups were found at baseline (table 1). A total of 46 patients completed the 6-month follow-up. Four patients were prematurely withdrawn from the test group: three because of implant loss and one because of elective abutment removal. Table 2 presents an overview of the primary and secondary outcomes.

Table 1. Baseline characteristics compared between groups

MIPS indicates minimally invasive Ponto surgery; LIT-TP, linear incision technique with soft tissue preservation

Variable	**MIPS** test group *number (%)*	**LIT-TP** control group *number (%)*
Gender		
Male	9 (36)	15 (60)
Female	16 (64)	10 (40)
Mean Age (SD) [a]	60 (13)	52 (13)
Ethnicity		
Caucasian	25 (100)	25 (100)
Smoking	5 (20)	4 (16)
Indication		
Acquired conductive/mixed	20 (80)	21 (84)
Congenital conductive	1 (4)	1 (4)
Single-sided deafness	4 (16)	3 (12)
Relevant diseases		
Diabetes Mellitus [b]	3 (12)	0 (0)
Skin disease	0 (0)	1 (4)
Chronic steroid use	0 (0)	1 (4)
Abutment length		
6 mm	1 (4)	0 (0)
9 mm	14 (56)	17 (68)
12 mm	10 (40)	8 (32)
Mean surgery time in minutes (SD)	6.4 (2.4)	20.8 (4.3)

[a] *A statistically significant higher age was found in the test group compared to the control group*

[b] *This concerns only patients with Diabetes Mellitus type II whom were treated with dietary restrictions and/or oral diabetes medication and had stable glucose levels*

Table 2. Outcome measures, compared between groups

MIPS indicates minimally invasive Ponto surgery; LIT-TP, linear incision technique with soft tissue preservation

Outcome measures	**MIPS** test group	**LIT-TP** control group	**P-value**
Sensibility at 6 months, mean % (SD)	n=21	n=25	
Total sensibility	99.6 (1.8)	98.0 (4.4)	0.17
Gnostic sensibility	99.2 (3.6)	96.7 (8.3)	0.30
Vital sensibility	100.0 (0.0)	99.3 (3.3)	1.00
Subjective numbness at 6 months, mean (SD)	n=21	n=25	
VAS-score	0.0 (0.0)	0.36 (1.1)	0.03
Area in mm^2	0.0 (0.0)	0.24 (0.8)	0.11
Skin dehiscence, N (%)	n=25	n=25	
7 days	16 (64)	0 (0)	<0.0001
21 days	8 (32)	0 (0)	0.004
12 weeks [a]	0 (0)	0 (0)	1.0
Soft tissue reactions according to Holgers, n (%) [b]	n=25	n=25	
No/Mild (Holgers 0-1)	23 (92)	18 (72)	
Adverse (Holgers 2-4)	2 (8)	7 (28)	0.14
POSAS Patient Scale at 6 months, mean (SD)	n=21	n=25	
Pain	1.6 (1.7)	2.7 (1.8)	0.005
Itching	2.4 (1.8)	2.5 (2.1)	0.94
Color [c]	1.3 (0.7)	2.9 (2.2)	0.006
Stiffness	1.4 (1.3)	2.6 (2.1)	0.002
Thickness	1.5 (1.4)	2.8 (2.7)	0.037
Irregularity	1.5 (1.1)	2.4 (2.3)	0.12
Overall opinion [d]	1.9 (1.8)	2.4 (2.3)	0.32
Total score	9.7 (5.1)	15.8 (10.8)	0.013
POSAS Observer Scale at 6 months, mean (SD)	n=21	n=25	
Vascularity	1.2 (0.7)	2.9 (1.3)	<0.0001
Pigmentation	1.0 (0.0)	2.2 (0.6)	<0.0001
Thickness	1.8 (1.2)	2.9 (1.6)	0.003
Relief	2.3 (1.6)	2.8 (1.3)	0.11
POSAS Observer Scale at 6 months, mean (SD)	n=21	n=25	
Pliability	1.8 (1.1)	2.2 (0.5)	0.009
Surface	1.1 (0.4)	2.3 (0.7)	<0.0001
Overall opinion	(0.8)	2.8 (1.2)	0.0001
Total score	10.8 (4.3)	15.3 (4.3)	0.001

ISQ values at 6 months, mean (SD)	n=21	n=25	
6-mm abutment –ISQ low [e]	70		
6-mm abutment – ISQ high [e]	72		
9-mm abutment – ISQ low	60.3 (2.2)	60.9 (2.3)	0.39
9-mm abutment – ISQ high	62.3 (2.3)	62.1 (2.6)	0.62
12-mm abutment – ISQ low	51.3 (3.2)	55.3 (3.5)	0.048
12-mm abutment – ISQ high	53.0 (3.2)	56.6 (3.9)	0.09
Change in ISQ 0-6 months, mean (SD)	n=21	n=25	
6-mm abutment – ISQ low [e]	8		
6-mm abutment – ISQ high [e]	4		
9-mm abutment – ISQ low	6.3 (2.4)	4.7 (2.1)	0.12
9-mm abutment – ISQ high	5.4 (1.7)	3.8 (2.2)	0.04
12-mm abutment – ISQ low	4.4 (3.3)	4.5 (1.9)	0.87
12-mm abutment – ISQ high	2.9 (3.0)	3.8 (2.8)	0.83
Sound processor use at 6 months, n (%)	n=21	n=25	
Daily users [f]	17 (81.0)	19 (76.0)	0.97
Implant loss 0-6 months, n (%)	n=25	n=25	
Implant loss	3 (12.0)	0 (0.0)	0.079

[a] n=22 for test group (3 implant losses) and n=25 for control group

[b] Referring to the highest score per patient up to 6 months after surgery

[c] n=15 for test group and n=25 for control group

[d] n=19 for test group and n=25 for control group

[e] Only one patient in the test group had a 6-mm abutment

[f] Per-protocol analysis is shown. In the intention-to-treat analysis daily use was 68% and 76% for patients in the test and control group respectively (p=0.75)

Skin sensibility and subjective numbness

At baseline, total sensibility was significantly better in the test group (100% versus 97%, p=0.0097), whereas subjective numbness was comparable between groups. At 21 days after surgery, mean total sensibility in the test group was 100% (SD 0) whilst a non-significant decrease in sensibility was observed in the control group (-4%, SD 7.5, p=0.055). At six months, mean total sensibility was 99.6% (SD 1.8) in the test group and 98.0% (SD 4.4) in the control group (p=0.16). Change in total sensibility from baseline to three weeks after surgery, and from baseline to six months after surgery, did not differ significantly between groups (p=0.079, p=0.52). At the six-month visit, no subjective numbness was reported in the test group, compared with a VAS-score of 0.36 (SD 1.1) in the control group. This resulted in significant better subjective numbness in the test group (p=0.034).

Surgery

All surgical procedures were performed without major perioperative complications or need for an intraoperative switch to an alternative surgical technique. Between groups, no difference in abutment length was observed. Surgery time was significantly shorter ($p<0.0001$) in the test group and was reduced by 69.2% compared with the control group (table 1).

Soft tissue outcomes

At the first visit after surgery, a minimal skin dehiscence was observed in 64% of the test group, whereas no dehiscences were reported in the control group ($p<0.0001$). These skin dehiscences consisted of a small macroscopic gap (at maximum a few millimeters) between skin and abutment, whereby, in some cases, bony tissue was visible on closer inspection. In case of such a dehiscence, prolonged application of antibiotic ointment was applied. In all patients, wound healing was completed within 12 weeks after surgery. Holgers grades across all visits are presented in figure 2. No differences in maximum Holgers scores ($p=0.084$) were found between groups across visits. Holgers 2 was the highest reported score in the test group and Holgers 3 in the control group. Adverse Holgers scores were observed in 8% of the patients in the test group and 28% of the patients in the control group, though this difference was not statistically significant (Table 2; $p=0.14$). Skin overgrowth and revision surgery were not observed in either group.

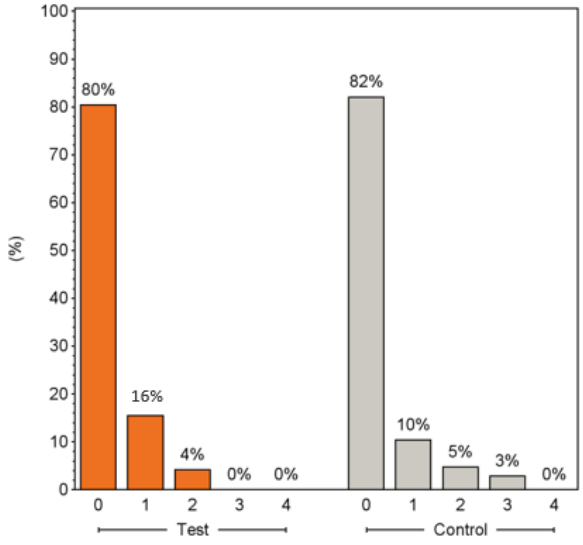

Figure 2. Soft tissue reactions according to Holgers, as a percentage across all visits including unplanned visits, separate for test and control group.

Holgers ≥ 2 is considered an adverse skin reaction.

Adverse events

Several adverse events were observed in both groups. Persistent itch (n=3), pain at the implant side (n=3), recurrent inflammation between visits (n=5), headache (n=3) and dizziness after surgery (n=2) were reported in the test group. These complaints resolved either spontaneously or after local treatment with antibiotic ointment, except for one patient in whom pain persisted until spontaneous implant loss occurred. In the control group, persistent itch and postoperative fever without signs of infection were reported in two patients. One patient complained of persistent pain, which was successfully treated with local antibiotic therapy. In the test group, five patients required one (n=4) or two (n=1) additional, unplanned visit(s). In the control group, seven patients required a single unplanned visit.

Cosmetic outcomes

The POSAS questionnaire was assessed at 21 days and 6 months after surgery, whereby no changes over time were observed in overall opinion and total score. At six months, the patient scale showed significant differences in favor of the test group for the categories pain, color, stiffness, thickness and total score, whereas the overall opinion was comparable between groups. Within the observer scale, significantly better scores were found for the test group in all categories except for the category relief.

Implant survival and stability

In the test group, three implants were lost within ten weeks after surgery: two spontaneous and one after trauma. This resulted in a statistically non-significant lower implant survival in the test group compared with the control group (p=0.08). None of the patients with implant loss smoked or suffered from diabetes mellitus type II. During follow-up, one abutment was removed in the test group because this patient was not satisfied with the BAHI. Abutment change (12 to 9 mm) was performed in another patient in the test group at six months follow-up, because she thought the abutment protruded too much. ISQ-values measured prior to abutment change were included in the six-month analysis. In the control group, neither implants nor abutments were lost or changed. When analyzing ISQ values per abutment length (figure 3), a higher ISQ-low was found for the 12-mm abutment in the control group at baseline and at six-months follow-up compared to the test group. ISQ-high was comparable between groups at all visits for abutment lengths 9 mm and 12 mm. Both ISQ-low and -high increased over time for all abutment lengths. A decrease of ISQ-high and ISQ-low was recorded for the two implants that subsequently were lost: ISQ-low declined with 13 and 9 points respectively. Both implants were lost within three weeks after the drop in ISQ was noticed.

Sound processor use

At six months, 17 patients in the test group and 19 patients in the control group used their sound processor daily (p=0.97, per-protocol analysis; p=0.75, intention-to-treat analysis). In these patients,

median use was 16 hours a day (range 4-16). For patients not wearing their sound processor every day, median use was 4.5 days per week in both test (4 patients, range 1-5 days) and control (6 patients, range 0-5 days) group.

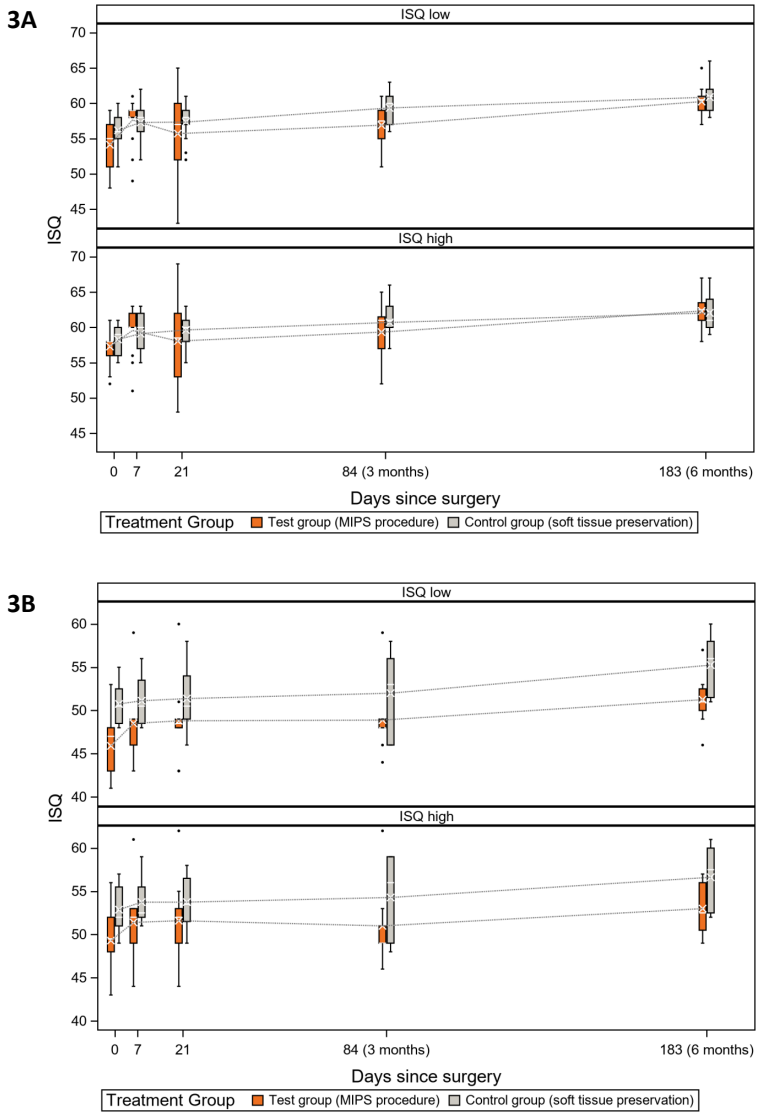

Figure 3. Boxplots of ISQ-low and -high over time for 9-mm (**3A**) and 12-mm (**3B**) abutment lengths.

The mean is marked by a cross and the median by a horizontal line. The boxplots represent the interquartile range and the dots represent outliers.

Discussion

Key findings

In this study, six-month clinical outcomes of MIPS were compared with the LIT-TP in order to assess the added value of MIPS. At six months, sensibility around the abutment and adverse soft tissue reactions were comparable between groups. In the MIPS group, a statistically significant shorter surgery time, significant better subjective numbness and cosmetic outcomes were observed. On the other hand, a statistically non-significant higher implant loss rate was reported in this group, and at one and three weeks after surgery, a statistically significant higher incidence of temporary, minimal, skin dehiscences.

Strengths and limitations

One of the major strengths of this study is that a new surgical technique was compared with the current standard procedure while all other variables were kept identical. Although no randomization was performed, all data was prospectively collected in a controlled setting, and both outcome measures and follow-up visits were identical between groups. A limitation might be that the surgeons were more experienced in performing the LIT-TP, since MIPS is relatively new. Also, sample size was based on the number of patients in the control group rather than statistical power calculations. Furthermore, patients with diseases or treatments known to influence bone quality were excluded and all included patients were, by chance, of Caucasian origin. In addition, surgeries were performed by two experienced surgeons exclusively in a tertiary referral center.

Evaluation of findings

At study initiation, it was hypothesized that sensibility would be favorable for the test group, since fewer cutaneous nerves will be damaged using MIPS. The primary outcome, total sensibility around the abutment at six months, was however comparable between groups. In contrast, subjective numbness was significantly better for MIPS at six months. The clinical relevance of this latter finding is debatable, since subjective numbness was only slightly better after MIPS and total skin sensibility was comparable between groups. Already 21 days after surgery, both total sensibility and subjective numbness were identical to sensibility prior to surgery in the MIPS group, whereas a non-significantly lower (albeit high) total sensibility and significantly worse subjective numbness were observed in the control group. At six months, skin sensibility approached 100% also for the control group, and no statistical significant difference between groups was found. This study therefore indicates that numbness is virtually gone as a side-effect of BAHIs.

When looking at secondary outcomes, surgery time was reduced with 69.2%. A faster surgical procedure is of course beneficial for both patient and surgeon. It is, however, uncertain whether this reduction in surgery time would also result in significantly higher production rates, since the total time needed in the OR, i.e. preparation time, is similar to the LIT-TP. MIPS also resulted in

improved subjective cosmetic outcomes compared with the LIT-TP, in line with the study of Calon et al. (10) It must however be noted that cosmetic outcomes were also good for the control group. Besides that, most patients found the POSAS questions rather difficult to answer because of limited visibility of the area around the abutment. This raises the question of whether these improved cosmetic outcomes are of clinical value. Interestingly, skin dehiscences were only reported after MIPS. These dehiscences might have been caused by an unnoticed shift of the skin biopsy after insertion of the cannula, prior to the drilling procedure. However, in the study of Calon et al., dehiscences were also reported in the LIT-TP. (10) Under-reporting of dehiscences in the control group of the present study might have contributed to the large difference in skin dehiscences between groups. All skin dehiscences were small and healed within three months after surgery. In case of a skin dehiscence, treatment with antibiotic ointment was pragmatically prolonged with two weeks, since the dehiscent skin could be a port of entry for bacteria and cause infection of the skin around the implant. Nevertheless, the number of adverse skin reactions did not differ between groups. Although these minimal skin dehiscences did not seem to have significant clinical impact in the current study, it is still important to report a dehiscence and consider whether treatment is necessary. Therefore, the recently developed IPS-scale might be an appropriate tool, since this soft tissue assessment scale scores skin integrity and provides treatment advice. (19) At this moment, however, the IPS-scale has not yet been validated.

In the light of the historical evolutions in implant design, implant loss rates have dropped from approximately 8.3% with the previous generation implants (20) to around 3% with the wide diameter implants. (13,21,22) Therefore, the non-significant, higher implant loss rate of 12% after MIPS is the most remarkable outcome of this study, whereby the two spontaneous implant losses are the most relevant. In particular, because (a statistically non-significant) higher implant loss rate after MIPS has also been reported in the study of Calon et al. We however need to be cautious when drawing conclusions regarding the higher implant loss after MIPS in these studies, because of insufficient statistical power for this secondary outcome. A possible contributory factor to the higher implant loss rate, is the limited visual control of the drill hole which might result in non-perpendicular insertion of the implant to the bone. A slight shift in the position of the cannula is hardly noticeable and might also result in a slightly off-centered placement of the implant and interposed soft tissue. Furthermore, the combination of two-step drilling and a limited space to provide cooling, might have resulted in a too high bone temperature causing thermal osteonecrosis. Thermal osteonecrosis might lead to resorption and thereby impaired osseointegration and decreased secondary implant stability. (23,24) On the other hand, Calon et al., used three-step drilling and reported the same number of implant loss after MIPS. (10)

Taking all the outcomes of the current study into consideration, we believe that at this moment, MIPS is not proven to be superior to the LIT-TP. We believe more research into MIPS and especially the associated implant loss is necessary, before this technique can be implemented as the standard

technique in our center. Also, long-term outcomes should be assessed and compared with the LIT-TP. In this regard, long-term 36-month results of the current study are expected in 2020. Furthermore, the drills used during MIPS have recently been modified in order to improve surgical outcomes. To evaluate this modified MIPS, a new prospective clinical trial is currently executed in our center.

Conclusion

MIPS has a shorter surgery time and better cosmetic outcomes in comparison to the LIT-TP. MIPS results in comparable skin sensibility at six months and similar soft tissue tolerability. The statistically non-significant higher implant loss rate of 12% after MIPS warrants more research into this surgical technique and its implications for osseointegration.

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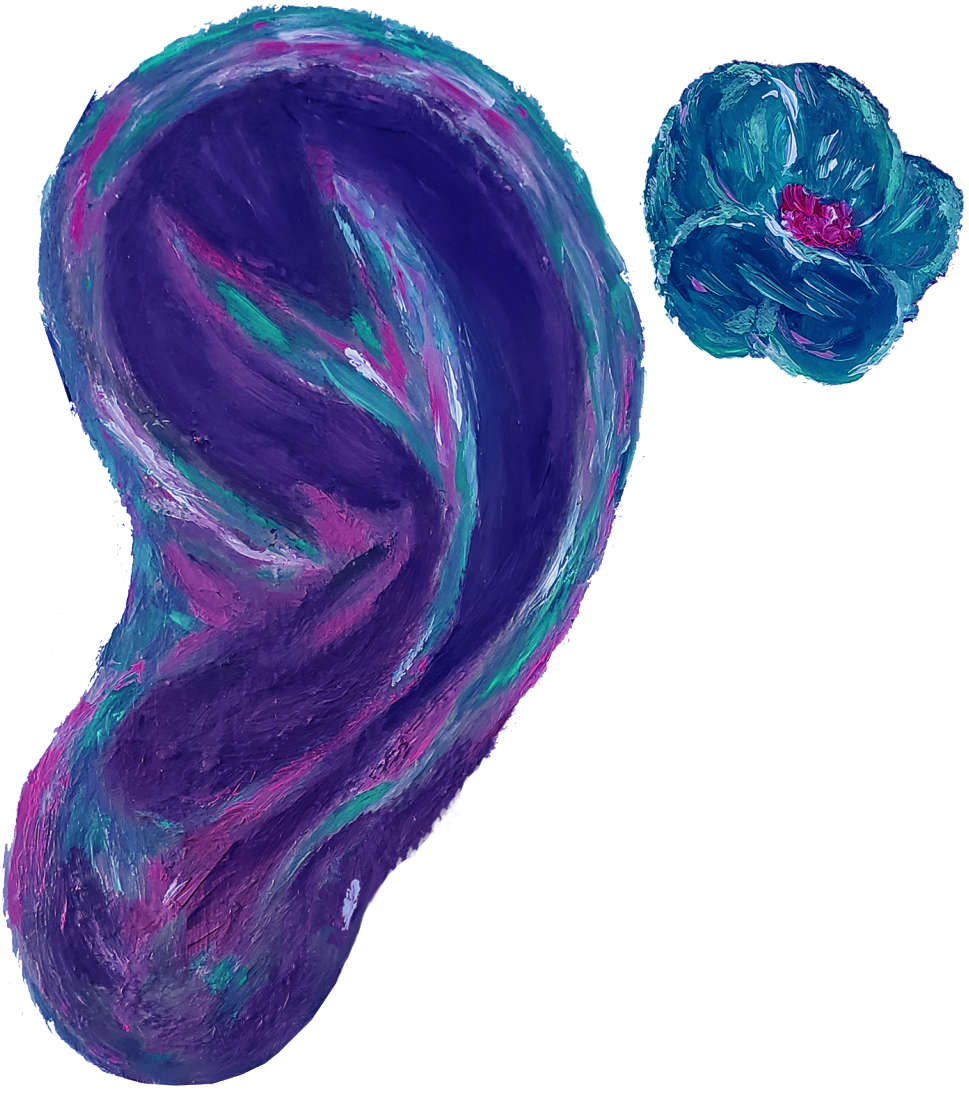

CHAPTER 5

A clinical evaluation of minimally invasive Ponto Surgery with updated procedure package for inserting bone-anchored hearing implants

Coosje J.I. Caspers
Ivo J. Kruyt
Emmanuel A.M. Mylanus
Myrthe K.S. Hol

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Abstract

Objective

To compare 6-months outcomes of the modified minimally invasive Ponto surgery (m-MIPS) to both the linear incision technique with soft tissue preservation (LIT-TP), and original MIPS (o-MIPS) for inserting bone-anchored hearing implants (BAHIs).

Study design

Exploratory pilot study with one test group and two historical control groups.

Setting

Tertiary referral center.

Patients

In the test group, 24 patients (25 implants) were prospectively included. Each control group comprised 25 patients (25 implants) who participated in previously conducted clinical trials.

Interventions

The test group received a BAHI using m-MIPS. The two control groups underwent surgery using the LIT-TP and o-MIPS, respectively.

Main outcome measures

Implant survival, implant stability and surgery-related variables were compared between the test and control groups. Soft tissue status, skin sensibility and subjective numbness were compared between m-MIPS and the LIT-TP only.

Results

Implant survival was comparable between m-MIPS and the LIT-TP, whereas implant stability measurements were slightly lower for m-MIPS. M-MIPS resulted in comparable adverse skin reactions and skin sensibility, significantly reduced surgical time and slightly improved subjective numbness, compared with the LIT-TP. Between m-MIPS and o-MIPS, no statistically significant differences in I implant survival, implant stability and surgical time were observed.

Conclusions

A trend towards lower implant loss rates after m-MIPS was observed, when compared with o-MIPS. M-MIPS seems to be a good alternative to the LIT-TP for inserting BAHIs, since most clinical outcomes were either comparable or slightly better for m-MIPS. Upon deciding on which technique to use, larger studies on implant survival should be performed. Furthermore, other aspects such as costs, training aspects and surgical experience should be evaluated.

Introduction

Because of its favorable postoperative outcomes, the linear incision technique with soft tissue preservation (LIT-TP) is currently considered the gold standard procedure to insert bone-anchored hearing implants (BAHIs). (1-4) To further reduce postoperative complications, a standardized punch-only procedure called minimally invasive Ponto surgery (MIPS) was developed in 2014. (5,6) Several institutions have already adopted this procedure notwithstanding the high variability in implant loss rates reported, ranging between 0% to 3.9% (6-9) and 12% to 35%. (10-12) The high implant loss rates in some studies raised concerns, especially since a non-significantly higher implant loss rate was found for MIPS when compared with the LIT-TP and bus-stop technique, respectively. (10,12) In line with this, a comparative study of MIPS and the LIT-TP conducted at our institution, resulted in a statistically non-significant though higher implant loss rate of 12% for MIPS. (13)

Several factors contributing to the high implant loss rates after MIPS have been proposed: 1) the presence of interposed periosteum, 2) incorrect angulation of the drill and/or implant, and 3) inadequate bone cooling resulting in thermal bone necrosis and thus impaired osseointegration. (10,12-14) The MIPS drills used in this study are included in an updated MIPS procedure pack available since November 2018 which is currently utilized in several institutions. The design and shape of the drill bits were modified to further improve drill efficiency and osteotomy preparation. (15) Additionally, 3-step drilling, as described in the surgical manual, was used instead of 2-step drilling in an attempt to reduce heat generation. To our knowledge, clinical outcomes of the modified MIPS drills (m-MIPS) have not yet been published. Since the modified drills are already in clinical use, we believe it is of importance to investigate the outcomes of m-MIPS, before determining whether this procedure should be considered an equivalent alternative to the LIT-TP. We have conducted an exploratory pilot study on clinical outcomes after m-MIPS, focusing on implant survival and stability. Outcomes were compared between m-MIPS and the LIT-TP (1), as well as between m-MIPS and MIPS with the original drill design (o-MIPS). (13)

Materials and Methods

Ethical considerations

This study was conducted with approval of the local ethical committee and performed according to the guidelines for Good Clinical Practice, ISO14155:2011, and the ethical principles stated by the Declaration of Helsinki. (16) All included patients provided written informed consent.

Study population

This study consisted of one test group and two control groups. Patients in the test group were prospectively included and underwent BAHI surgery using m-MIPS. Patients in the control groups were already implanted with a BAHI in two previously conducted prospective clinical trials, whereby the LIT-TP had been performed in control group 1 (1,2) and o-MIPS in control group 2. (13) Study design, in- and exclusion criteria, outcome measures and follow-up visits were identical among the three groups. (1,13) External monitoring was conducted in all studies.

Surgical techniques and follow-up

In all patients, the Wide Ponto implant® (diameter 4.5mm, length 4.0mm, Oticon Medical AB, Askim, Sweden) with abutment (6, 9, or 12mm) was inserted in a one-stage surgery. All surgeries were performed by experienced ENT-surgeons (EM and MH). Abutment length was chosen based on skin thickness at the implant site, as measured prior to local infiltration.

In the test group, m-MIPS was conducted (figure 1). With this technique, a circular incision is made with a 5-mm biopsy punch, where after periosteum is removed with a raspatorium. A cannula is inserted, through which 3-step drilling is performed during continuous irrigation with saline solution and with flushing of the cannula between the drill steps. Three-step drilling consists of the following steps: 1) a guide hole is created using the cannula guide drill with spacer, 2) the hole is deepened for a 4-mm implant using the same drill without spacer, 3) the hole is widened with the cannula widening drill. The cannula is then removed and the implant with premounted abutment is inserted. An insertion indicator is used to check whether full implant insertion is established. If this is not achieved, the implant is manually tightened.

In control group 1, the LIT-TP group, a linear incision has been made down to the periosteum of the skull bone. (17) After periosteum removal, a 2-step drilling sequence was performed whereby the guide hole was created to full depth in one step prior to widening of the hole. Following implant-abutment insertion, the skin was closed with sutures and a 5-mm punch hole was created to enable the abutment to penetrate the skin. (18) In control group 2, o-MIPS has been performed. This procedure differed from m-MIPS in two aspects: 1) a previous generation drill design was used and 2) 2-step drilling was performed instead of 3-step drilling.

The 2-step drilling sequence, as conducted in the two control groups, represents a deviation from the standard 3-step drilling sequence, recommended by the manufacturer. This 2-step drilling protocol was however performed because, at our tertiary referral center, this procedure is known for its excellent outcomes. (2,19)

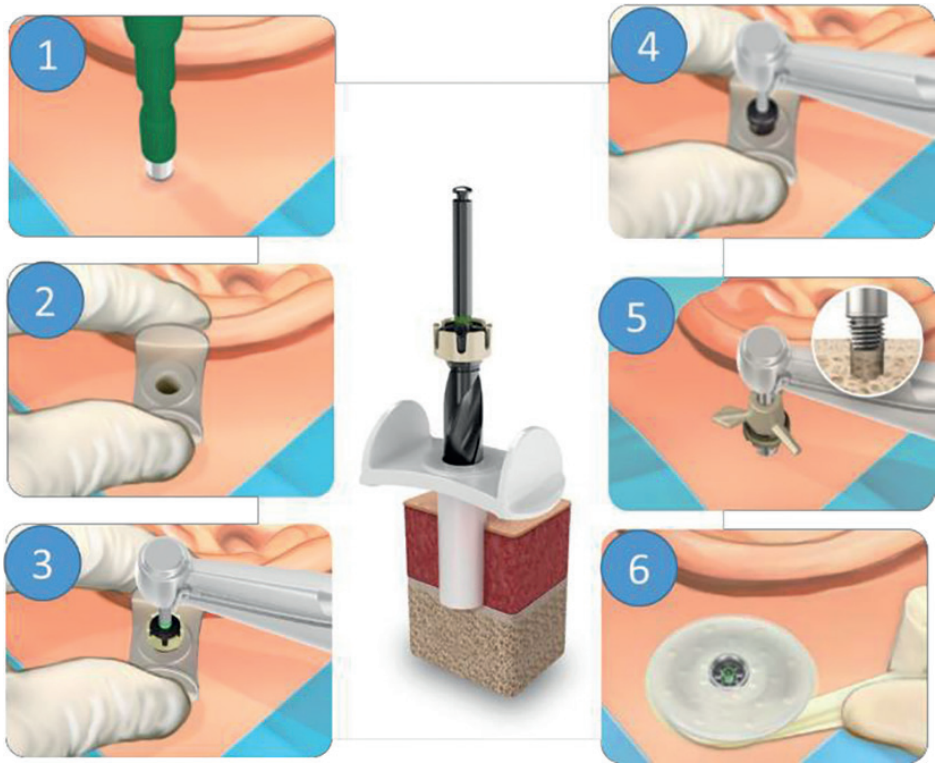


Figure 1. Modified minimally invasive Ponto surgery: 1) a circular incision is created using a 5-mm biopsy punch. 2) The cannula is inserted. 3,4) Three-step drilling is performed. 5) The cannula is removed and the implant is inserted. 6) A healing cap with dressing is attached to the abutment.
Image provided by Oticon Medical ™. Reprinted with permission.

The aftercare was identical in all groups. Directly after surgery, a healing cap and antibiotic dressing containing hydrocortisone, oxytetracycline and polymyxin-B (Terra-Cortril®) was fixed onto the abutment. Seven days postoperatively, the healing cap was removed and topical application of Terra-Cortril® ointment around the abutment was prescribed twice daily for two weeks. Further follow-up visits were scheduled at 21 days (including sound processor fitting), 12 weeks, and 6 months after surgery.

Outcome measures

Main outcome measures were implant survival and stability. Furthermore, surgical time and intraoperative complications were assessed. These outcomes were compared between m-MIPS and the LIT-TP, as well as between m-MIPS and o-MIPS. In addition, soft tissue status, skin sensibility around

the abutment, subjective numbness and sound processor use were compared between m-MIPS and the LIT-TP. Unplanned visits, need for revision surgery and adverse events were recorded.
To assess implant stability, the Implant Stability Quotient (ISQ) was determined by means of resonance frequency analysis directly after complete implant insertion, and at every follow-up visit.(1,2,20) For these measurements, the Osstell® ISQ device (Osstell AB, Göteborg, Sweden) and a SmartPeg (type 55) were used. Perpendicular measurements were performed and reported as the highest and lowest scores. Surgical time (in minutes) was defined as punch to complete implant insertion for both o-MIPS and m-MIPS, and as incision to placement of the last suture for the LIT-TP. Soft tissue tolerability was assessed by both the Holgers classification (21) and the IPS-scale. The IPS-scale is a new soft tissue assessment scale which includes a standardized treatment advice. (22) Because of its recent introduction, the IPS-score was retrospectively assessed in the LIT-TP group. A Holgers ≥ 2 or IPS score indicating treatment were considered adverse skin reactions. The presence of a skin dehiscence was also reported. For the m-MIPS group, the size of the dehiscence was described in millimeters.

Skin sensibility around the abutment was measured according to the previous trials in which the two control groups participated. (1,2,13) Hereby, gnostic and vital sensibility were both tested at six standardized locations around the abutment. (1) For this purpose, a broken cotton swab was used; gnostic sensibility was assessed by using the soft end, and vital sensibility was assessed by using the sharp end. The percentage of correct responses was reported and compared between m-MIPS and the LIT-TP. Subjective numbness was assessed by means of a Visual Analogue Scale (VAS) ranging from 0 (no numbness) to 10 (complete numbness).

Statistical analysis

Achieving the determined sample size for a statically powered study on implant survival was unfortunately not feasible due to the low implant loss rates after BAHI surgery and the small number of patients with an indication for a BAHI. Therefore, we chose to perform an exploratory pilot study with the sample size of the test group set at 25 patients. This sample size was in line with the sample sizes of the control groups. (1,2,13) Data analysis was performed using both intention-to-treat (ITT) and per-protocol (PP) populations. For statistical analysis, nonparametric tests were used. Groups were compared using the Fishers nonparametric permutation test for numbness variables, the Mann-Whitney U-test for continuous variables, the Mantel Haenzsel chi-square test for ordered categorical variables, the Chi-square test for nonordered categorical variables, and the Fisher's exact test for dichotomous variables. Changes over time were analyzed using the Wilcoxon signed rank test for continuous variables, and the Sign test for dichotomous and ordered categorical variables. The Logrank survival test was used to compare implant survival between groups. In case of premature withdrawal, all collected data to the point of withdrawal were included in the analysis. For the primary variable, missing data were handled using the last-observation-carried-forward method. In case of bilaterally implanted patients, patient characteristics were handled on

patient-level, and implant-related characteristics on implant-level. Patients who were included in both test group and control group 2 were treated as two separate subjects in the analysis.
Data analysis were performed by independent external biostatisticians (Statistika Konsultgruppen, Göteborg, Sweden) and conducted according to a predefined statistical plan. According to the predefined plan, no corrections for multiplicity were performed. All statistical tests were two-tailed, conducted at a 0.05 significance level and carried-out using SAS® v9.4 (Cary, NC).

Results

Patient population

In the m-MIPS group, 24 patients (25 implants) were included between September 2018 and June 2019. In the LIT-TP and o-MIPS group, 25 patients (25 implants) were included between February and August 2014, and between June and December 2017, respectively. (1,13) Two patients underwent sequential bilateral implantation and were included in both the o-MIPS and m-MIPS group. No baseline differences were found between the test and the two control groups (table 1). Out of the 74 included patients, five patients did not complete the 6-month follow-up because of implant loss (one in m-MIPS group and three in o-MIPS group) and abutment removal (one in o-MIPS group). Six patients were excluded from the PP population, comprising the five prematurely withdrawn patients, and one bilaterally implanted patient who was five weeks late for the 6-month visit after m-MIPS. Below, outcomes of the ITT population are described (see also table 2). Outcomes of the PP population are presented in supplemental digital content 1.

Surgery

All surgical procedures were performed without major intraoperative complications (table 1) or conversions to another surgical technique. Compared with the LIT-TP, m-MIPS reduced the previously defined "surgical time" with 70% ($p<0.0001$). Surgical time for m-MIPS and o-MIPS was comparable.

Unplanned visits and adverse events

In all patients, a total of 16 unplanned visits, 10 surgery-related and 15 implant-related adverse events were reported (table 2). All adverse events were considered mild to moderate and resolved either spontaneously or with the use of local antibiotic ointment.

Table 1. Patient and surgical characteristics for the test group and two control groups.

MIPS indicates minimally invasive Ponto surgery; m-MIPS, modified MIPS; o-MIPS, original MIPS; LIT-TP, linear incision technique with soft tissue preservation; SD, standard deviation.

Variable [a]	**m-MIPS** test group	**LIT-TP** control group 1	**o-MIPS** control group 2
Patient variables	n=24	n=25	n=25
Gender, n (%)			
Male	9 (38)	15 (60)	9 (36)
Female	15 (63)	10 (40)	16 (64)
Age in years, mean (SD)	53 (14)	52 (13)	60 (13)
Ethnicity, n (%)			
Caucasian	23 (96)	25 (100)	25 (100)
Hispanic	1 (4)	0 (0)	0 (0)
Smoking, n (%)	6 (25)	4 (16)	5 (20)
Relevant diseases, n (%)			
Diabetes Mellitus [b]	3 (13)	0 (0)	3 (12)
Skin disease	1 (4)	1 (4)	0 (0)
Chronic steroid use	0 (0)	1 (4)	0 (0)
Indication, n (%)			
Acquired conductive/mixed	17 (71)	21 (84)	20 (80)
Congenital conductive	0 (0)	1 (4)	1 (4)
Single-sided deafness	7 (29)	3 (12)	4 (16)
Bilateral implantation, n (%)	1 (4)	0 (0)	0 (0)
Surgical (implant) variables	n=25	n=25	n=25
Intraoperative complication, n(%)			
Drilling into vein	2 (8)	4 (16)	2 (8)
Dura mater exposed	1 (4)	2 (8)	0 (0)
Difficult implant insertion [c]	3 (6)	0 (0)	0 (0)
Abutment length, n (%)			
6 mm	1 (4)	0 (0)	1 (4)
9 mm	14 (56)	17 (68)	14 (56)
12 mm	10 (40)	8 (32)	10 (40)
Surgery time in minutes, mean (SD)	6.2 (2.7)	20.8 (4.3)	6.4 (2.4)

[a] *Variables were compared between modified MIPS and LIT-TP, and between modified MIPS and original MIPS.*

[b] *Type 2 diabetes mellitus with stable blood glucose levels and treatment with dietary restrictions and/or oral diabetes medication.*

[c] *Implant needed to be repositioned in the existing punch-hole because of incomplete insertion (two cases) or an incorrect angle (one case).*

Table 2. Outcome measures compared between test and control groups. Results are presented for the ITT population.

MIPS indicates minimally invasive Ponto surgery; m-MIPS, modified MIPS; o-MIPS, original MIPS; LIT-TP, linear incision technique with soft tissue preservation; SD, standard deviation; VAS, visual analogue scale; AUC, area under the curve; ISQ, implant stability quotient.

Outcome measure	**m-MIPS** test	**LIT-TP** control 1	**p-value** m-MIPS vs LIT-TP	**o-MIPS** control 2	**p-value** m-MIPS vs o-MIPS
Implant loss 0-6 months, n (%)	n=25	n=25		n=25	
Implant loss	1 (4.0)	0 (0.0)	0.32	3 (12.0)	0.30
AUC ISQ 0-6 monhts, mean (SD)	n=25	n=25			
6-mm abutment, ISQ-low [a]	69.0			68.3	
6-mm abutment, ISQ-high [a]	69.2			70.6	
9-mm abutment, ISQ-low	57.1 (2.8)	59.1 (2.2)	0.065	57.1 (3.3)	0.87
9-mm abutment, ISQ-high	58.6 (2.4)	60.6 (2.4)	0.041	59.5 (3.5)	0.35
12-mm abutment, ISQ-low	48.8 (3.5)	52.8 (3.9)	0.10	48.9 (4.1)	0.34
12-mm abutment, ISQ-high	50.5 (3.1)	54.8 (3.7)	0.037	51.3 (3.9)	0.97
Maximum Holgers 0-6 months, n (%) [b]	n=25	n=25			
0	18 (72)	11 (44)			
1	5 (20)	7 (28)			
2	2 (8)	4 (16)			
3	0 (0)	3 (12)			
4	0 (0)	0 (0)	0.028		
Maximum I-, P-, S-scores 0-6 months, n (%) [b]	n=25	n=25			
I-score (inflammation)					
0	5 (21)	12 (48)			
1	17 (71)	7 (28)			
2	2 (8)	2 (8)			
3	0 (0)	4 (16)			
4	0 (0)	0 (0)	0.87		

Table 2. Continued

Outcome measure	**m-MIPS** test	**LIT-TP** control 1	**p-value** m-MIPS vs LIT-TP	**o-MIPS** control 2	**p-value** m-MIPS vs o-MIPS
P-score (Pain)					
0	20 (83)	15 (60)			
1	4 (17)	10 (40)			
2	0 (0)	0 (0)	0.11		
S-score (Skin height)					
0	23 (96)	17 (68)			
1	1 (4)	8 (32)			
2	0 (0)	0 (0)	0.027		
Sensibility at 6 months, mean % (SD) [c]	n=25	n=25			
Total sensibility	100 (0.0)	98.0 (4.4)	0.048		
Gnostic sensibility	100 (0.0)	96.7 (8.3)	0.11		
Vital sensibility	100 (0.0)	99.3 (3.3)	1.00		
Subjective numbness at 6 months, mean (SD)	n=24	n=25			
VAS	0.21 (1.0)	0.36 (1.1)	0.12		
Sound processor use at 6 months	n=24	n=25			
Daily users, n (%)	23 (96)	19 (76)	0.11		
Reason unplanned visit, n					
Pain at implant side	1	2		0	
Inflammation at implant side	1	4		2	
Implant loss	1	0		3	
Abutment removal	0	0		1	
Postoperative fever	0	1		0	

Implant-related adverse event, n			
Pain at implant side	1	1	3
Recurrent inflammation at implant side	2	0	3
Bleeding around implant	2	0	0
Small wound next to abutment	0	0	1
Persistent itch	1	0	2
Surgery-related adverse event, n			
Postoperative fever	0	1	0
Postoperative headache	4	0	2
Postoperative dizziness	1	0	2

[a] Only two 6-mm abutments were used, one in the modified MIPS group and one in the original MIPS group.

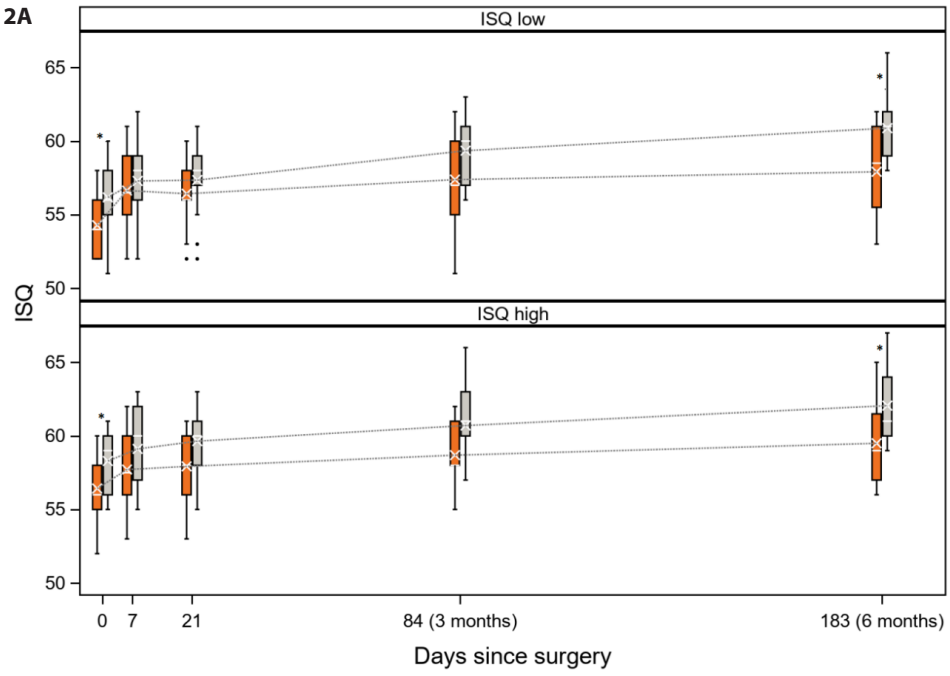
[b] All visits including unplanned visits.

[c] Last-observation-carried-forward (LOCF) method was used. Without LOCF, mean total, gnostic and vital sensibility were similar, but the p-values were slightly different (p=0.057 for total sensibility, p=0.11 for gnostic sensibility and p=1.00 for vital sensibility).

Implant survival and stability

In the m-MIPS group, one implant was lost within ten weeks postoperatively, preceded by complaints of pain. In the LIT-TP no implant loss occurred, and in the o-MIPS three implants were lost (two spontaneous, one after trauma), all within ten weeks postoperatively. No significant differences in implant loss were observed between m-MIPS and LIT-TP (p=0.32), nor between m-MIPS and o-MIPS (p=0.30). In both the m-MIPS and o-MIPS group, a change to a shorter abutment was performed in one patient because of complaints related to too much protrusion. Furthermore, one abutment was removed in the o-MIPS group due to the patient being unsatisfied with the BAHI.

For the 9-mm and 12-mm abutment, the mean 0-6 month area under the curve (AUC) of the ISQ-high was significantly higher for the LIT-TP compared with m-MIPS, whereas the 0-6 month ISQ-low was comparable between groups (table 2). Similar 0-6 month AUC ISQ values were found for m-MIPS and o-MIPS. For m-MIPS and the LIT-TP, ISQ values were either similar or slightly lower for m-MIPS, depending on the time point of assessment (figure 2). For m-MIPS and o-MIPS, ISQ-high and -low were comparable across visits. ISQ-high and -low improved significantly over time in all three treatment groups.



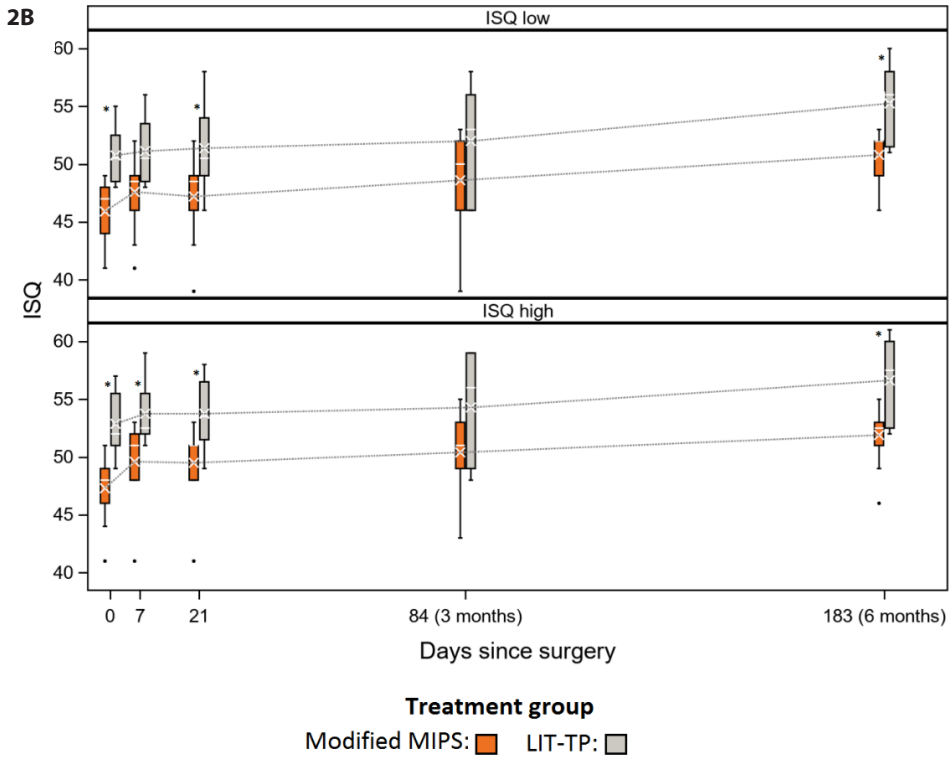


Figure 2. ISQ values for the modified MIPS (in orange) and LIT-TP (in grey) group at baseline, 7 days, 21 days, 3 months and 12 months after surgery for the 9-mm (**2A**) and the 12-mm abutment (**2B**).

The mean is marked by a cross and the median by a horizontal line. The boxplots represent the interquartile range and the dots represents outliers. MIPS indicates minimally invasive Ponto surgery; LIT-TP, linear incision technique with soft tissue preservation.

Soft-tissue status

A skin dehiscence was observed in 72% of the m-MIPS patients but in none of the LIT-TP patients ($p<0.0001$). All skin dehiscences consisted of a small gap between the abutment surface and the surrounding skin with a median width of 2 mm (range 0.5-3 mm). The patients with skin dehiscence did not experience any discomfort. At the 12-week visit all skin dehiscences were healed. Within this time period, no adverse Holgers scores were observed in these patients. Holgers and IPS scores across visits are presented in figure 3. The Holgers scores differed significantly between groups at 6 months, with worse scores for the LIT-TP group ($p=0.049$). In line with this, maximum Holgers across visits were higher for LIT-TP (table 2). Furthermore, albeit not reaching statistical significance, adverse Holgers scores were reported in 8% and 28% of the m-MIPS and LIT-TP group, respectively ($p=0.14$). A significant difference in the distribution of total IPS-scores was found between m-MIPS

and LIT-TP at 7 days, 21 days and 12 weeks after surgery ($p<0.0001$ at 7 days; $p=0.0007$ at 21 days and $p<0.0081$ at 12 weeks). A statistically higher Inflammation (I)-score was found for m-MIPS at 7 and 21 days, and a statistically higher Skin height (S)-score and I-score for LIT-TP at 12 weeks and 6 months, respectively. The Pain (P)-score did not differ between groups. Across all visits, the maximum I- and P-score did not differ significantly between groups, whereas the maximum S-score was significantly higher for LIT-TP ($p=0.027$; table 2). When comparing adverse IPS-scores at the different visits, no statistical difference was found between groups. Across visits, adverse IPS-scores were reported in 17% and 36% of the m-MIPS and LIT-TP group, respectively ($p=0.23$). All adverse skin reactions were successfully treated with antibiotic ointment. None of the patients required revision surgery.

Sensibility and subjective numbness

Total sensibility across visits is presented in figure 4. At baseline, mean total sensibility was significantly better for m-MIPS compared with the LIT-TP (100% versus 97%, $p=0.009$). At 21 days after surgery, sensibility had decreased in both groups with a significantly higher sensibility for m-MIPS (97.7% versus 93%, $p=0.017$). At 6 months, skin sensibility was also favorable for m-MIPS (table 2). However, change in sensibility from baseline to 21 days and 6 months did not significantly differ between groups. In general, skin sensibility was back to baseline sensibility at 12 weeks for m-MIPS and at 6 months for the LIT-TP, respectively. It must however be noted that skin sensibility was not measured in the LIT-TP group at the 12 week visit. VAS scores for subjective numbness were at baseline levels at 21 days for m-MIPS and at 6 months for the LIT-TP. Subjective numbness was significantly better for m-MIPS at 21 days (VAS 0.2 (SD 1.0) versus VAS 2.2 (SD 2.7); $p<0.001$), and comparable between groups at 6 months (table 2).

Sound processor use

Sound processor use is presented in table 2. For the seven patients who did not use their sound processors on a daily base, the median use was 4 days a week (range 0-5).

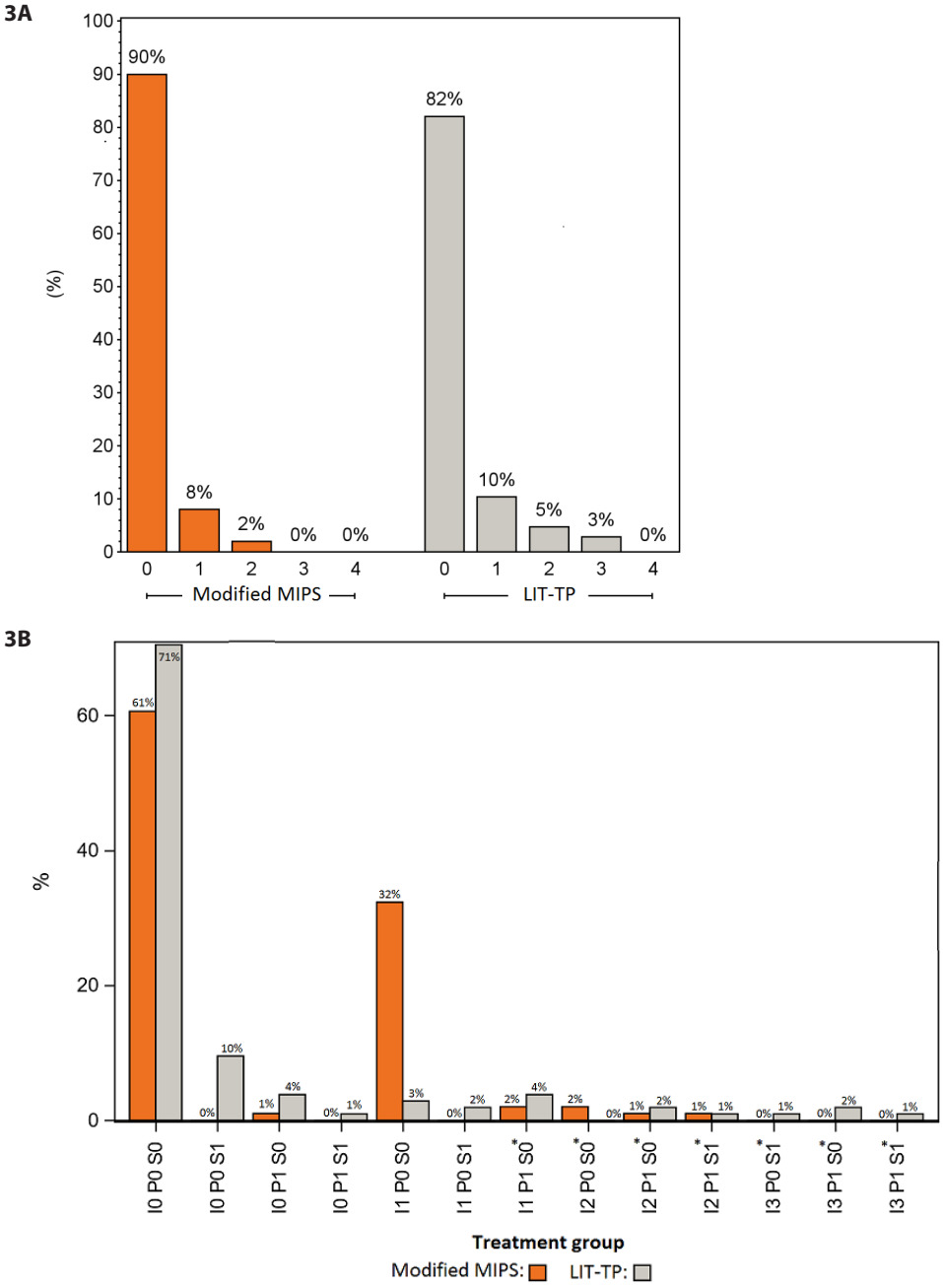


Figure 3. Soft tissue reactions across all visits according to the Holgers scale (**3A**) and the IPS-scale (**3B**) for the modified MIPS group (orange) and LIT-TP group (grey).

Holgers ≥ 2 and IPS scores indicating treatment were considered to be adverse skin reactions. Adverse IPS scores are marked with an asterisk. MIPS indicates minimally invasive Ponto surgery; LIT-TP, linear incision technique with soft tissue preservation.

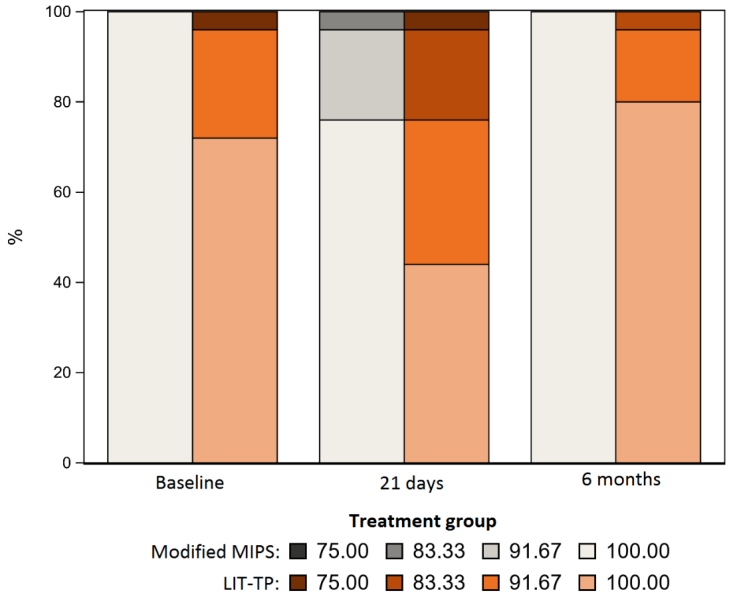


Figure 4. Total skin sensibility around the abutment at baseline, 21 days and 6 months after modified MIPS (presented in grey) and LIT-TP (presented in orange).

MIPS indicates minimally invasive Ponto surgery; LIT-TP, linear incision technique with soft tissue preservation.

Discussion

In terms of intra- and postoperative complications, both minimally invasive Ponto surgery (MIPS) and the linear incision technique with soft tissue preservation (LIT-TP) come across as safe techniques to insert BAHIs. Implant survival after 6-month follow-up was comparable between groups with an implant survival rate of 96% for m-MIPS and 100% for the LIT-TP. M-MIPS significantly reduced surgical time with 70%, compared with the LIT-TP, whereas adverse skin reactions across visits and sound processor use were comparable between these groups. With regards to skin sensibility, our data suggest that numbness is no longer a postoperative side effect of BAHI surgery when using tissue-preserving techniques including MIPS., When comparing m-MIPS and o-MIPS, no statistically significant differences in implant stability, survival, surgical time and intraoperative complications were found.

Highly variable implant loss rates have been reported for o-MIPS in the literature. (6-12) Our findings might show a tendency towards lower implant loss rates with m-MIPS compared with o-MIPS, with implant loss rates of 4% versus 12%. It is plausible these findings are attributed to the modified drill design in combination with the use of the 3-step drilling sequence.

Strengths and limitations

This is the first study to evaluate clinical outcomes of m-MIPS and to compare these to outcomes of the LIT-TP and o-MIPS. All data was prospectively collected and all patients were scheduled according to an identical follow-up scheme. Additionally, outcomes were measured in a standardized manner. Due to the use of historical control groups, randomization and a blinded follow-up were not possible. Sample size of the test group was determined based on the number of patients in the control groups rather than a statistical power calculation.

Interpretation of findings

In a preclinical study comparing the drill set design of m-MIPS and o-MIPS, the modified drills were found to generate significantly less heat, except in cases of impaired irrigation where they performed equally. (15) In line with this, a low implant loss rate of 4% was found for m-MIPS in the current study, whereas an implant loss rate of 12% was previously found for o-MIPS. Although a follow-up of 6 months seems relatively short, in previous publications on o-MIPS, all implant losses occurred within 3 months after implantation. (10-13) These early implant losses support the hypothesis that implant loss after o-MIPS may be a result of impaired osseointegration caused by overheated bone. A recent in vitro study evaluating drill components used for BAHI surgery demonstrated the dependence of temperature increase during ostomy preparation on multiple factors such as drill design, irrigation and drilling procedure. (23) The combination of the modified drill design and the 3-step drilling protocol with adequate irrigation, therefore seems promising with regards to implant survival. On the other hand, caution is required when drawing firm conclusions regarding implant loss rates. One could argue however, based on this exploratory pilot study, a trend towards better implant survival might be expected using m-MIPS compared to o-MIPS. In order to draw firm conclusions, further research on (long-term) implant survival with adequate sample sizes is warranted.

As for ISQ-measurements, both the ISQ-high and -low were significantly lower for m-MIPS compared with the LIT-TP at several follow-up visits. Additionally, the mean 0-6 month AUC of the ISQ-high was significantly lower for m-MIPS as well. The meaning and relevance of individual ISQ-values is subject to debate and individual values should therefore not be interpreted.(20) The trend in ISQ-values over time in a population is thought to be a more relevant measure of implant stability. (20) In all three study groups, both ISQ-low and -high did increase over time.

The current outcomes on skin sensibility and soft tissue status after m-MIPS, in comparison with the LIT-TP, are in line with previously conducted studies comparing o-MIPS and the LIT-TP, with better subjective numbness for MIPS and comparable skin sensibility and adverse skin reactions between groups. (12,13) Significantly lower maximum Holgers scores and a trend towards fewer adverse Holgers scores were observed for m-MIPS compared with the LIT-TP. A reduction in adverse skin reactions with m-MIPS seems reasonable, since tissue damage is minimal and the vascularity

surrounding the implant is left intact. The tendency towards fewer adverse Holgers scores has been observed in studies evaluating o-MIPS as well, but no significant differences have been found when compared with the LIT-TP. (12,13) In this study, the IPS scale was also used. (22) Whereas the Holgers scale was designed to determine soft tissue status at 3 months after implantation, the IPS scale was developed to assess inflammation, as well as skin height and the presence of pain at any moment after surgery. These differences are reflected by the number of adverse skin reactions according to each scale: adverse IPS scores were reported more frequently than adverse Holgers scores. The I-score, which includes the parameter skin integrity, was significantly higher for m-MIPS at 7 days and 21 days after surgery, due to the high incidence of skin dehiscences. The higher S-scores at 12 weeks for the LIT-TP all concerned S1 scores, indicating that revision surgery was not required. The higher I-scores for the LIT-TP at 6 months corresponded with higher Holgers scores in this group, suggesting the presence of erythema, edema or granulation tissue in these patients.

Other considerations

When deciding whether BAHIs should be inserted with m-MIPS or with the LIT-TP, we believe it is important to take aspects like costs, training, surgical experience and perhaps also patients´ preferences, into account. Surgical time is shorter for m-MIPS compared with the LIT-TP and a reduction of costs might therefore be expected. On the other hand, the total time spent in the operation theater and equipment-related costs should also be taken into consideration. When training surgical residents, or when performing BAHI surgery in (especially young) patients with thin cranial bones or cranial malformations, m-MIPS may be a less appropriate technique. Furthermore, when performing m-MIPS, experience with the LIT-TP is of importance since conversion to an open technique could be required, for example in case of a major bleeding. (7)

Conclusion

In this exploratory pilot study, minimally invasive Ponto surgery and the linear incision technique with soft tissue preservation both resulted in favorable clinical outcomes with low intra- and postoperative complication rates and are considered safe techniques to insert BAHIs. A tendency towards lower implant loss rates was observed when using the second generation of MIPS (m-MIPS), when compared to the first generation. Therefore, m-MIPS seems be a good alternative to the LIT-TP. However, upon deciding on which technique to use, data of long-term studies with adequate sample sizes and cost-benefit studies are necessary.

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Supplemental material

Supplemental digital content 1, Table. Outcome measures compared between test and control groups. Results are presented for the PP population.

MIPS indicates minimally invasive Ponto surgery; m-MIPS, modified MIPS; o-MIPS, original MIPS; LIT-TP, linear incision technique with soft tissue preservation; SD, standard deviation; AUC, area under the curve; ISQ implant stability quotient; VAS, visual analogue scale.

Outcome measure	**m-MIPS** test	**LIT-TP** control 1	**p-value** m-MIPS vs LIT-TP	**o-MIPS** control 2	**p-value** m-MIPS vs o-MIPS
AUC 0-6 months, mean (SD)	n=22	n=25		n=21	
6-mm abutment –ISQ low [a]	69.0			68.3	
6-mm abutment – ISQ high [a]	69.2			70.6	
9-mm abutment – ISQ low	57.8 (2.7)	59.1 (2.2)	0.28	58.0 (2.6)	0.78
9-mm abutment – ISQ high	58.9 (2.5)	60.6 (2.4)	0.14	60.2 (3.1)	0.17
12-mm abutment – ISQ low	48.8 (3.5)	52.8 (3.9)	0.10	49.6 (4.0)	0.51
12-mm abutment – ISQ high	50.5 (3.1)	54.8 (3.7)	0.037	51.7	0.89
Maximum Holgers 0-6 months, n (%) [b]	n=22	n=25			
0	17 (77)	11 (44)			
1	4 (18)	7 (28)			
2	1 (5)	4 (16)			
3	0 (0)	3 (12)			
4	0 (0)	0 (0)	0.009		
Maximum I-, P-, S-scores 0-6 months, n (%)	n=22	n=25			
I-score (Inflammation)					
0	5 (23)	12 (48)			
1	16 (73)	7 (28)			
2	1 (5)	2 (8)			
3	0 (0)	4 (16)			
4	0 (0)	0 (0)	0.74		

Supplemental digital content 1, Table. Continued

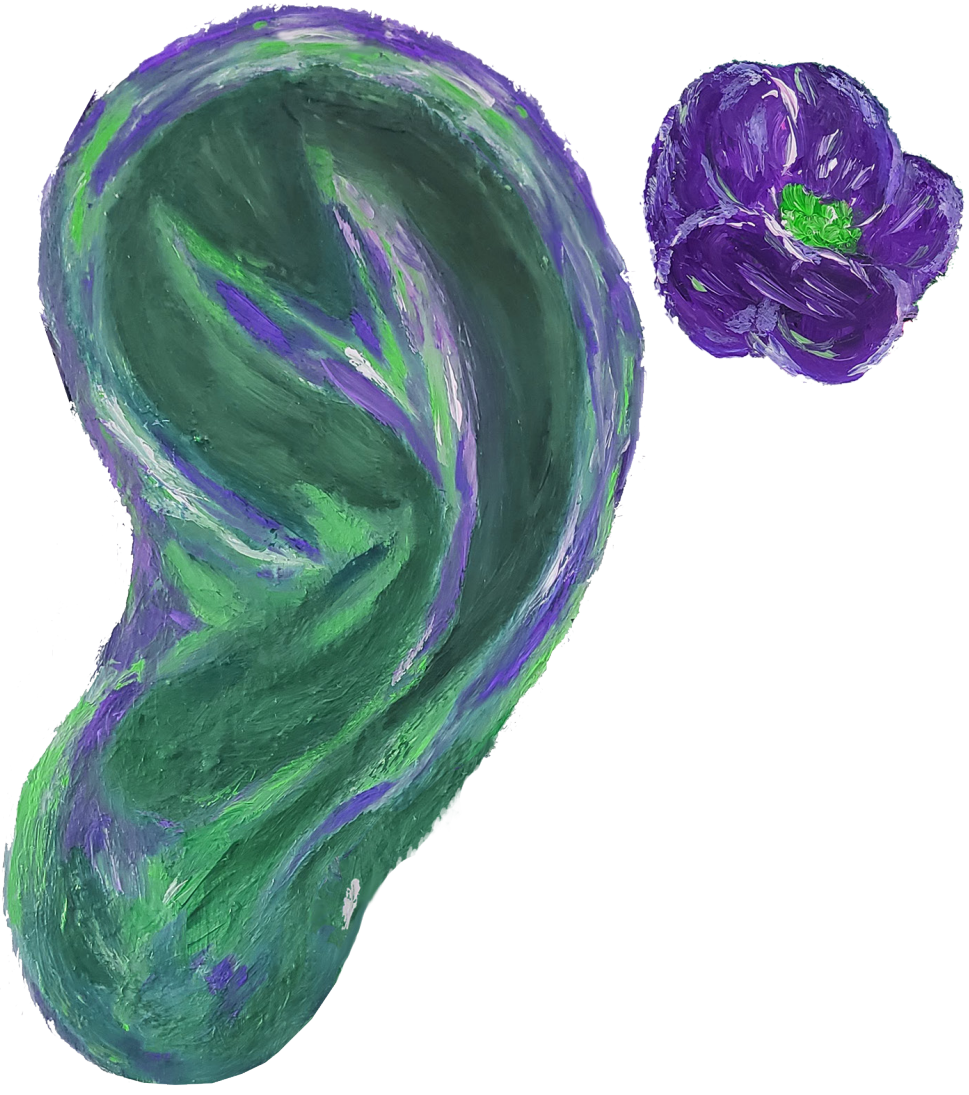
Outcome measure	m-MIPS test	LIT-TP control 1	p-value m-MIPS vs LIT-TP	o-MIPS control 2	p-value m-MIPS vs o-MIPS
P-score (Pain)					
0	20 (91)	15 (60)			
1	2 (9)	10 (40)			
2	0 (0)	0 (0)	0.02		
S-score (Skin height)					
0	22 (100)	17 (68)			
1	0 (0)	8 (32)			
2	0 (0)	0 (0)	0.007		
Sensibility at 6 months, mean % (SD)	n=22	n=25			
Total sensibility	100 (0.0)	98.0 (4.4)	0.07		
Gnostic sensibility	100 (0.0)	96.7 (8.3)	0.14		
Vital sensibility	100 (0.0)	99.3 (3.3)	1.00		
Subjective numbness at 6 months, mean (SD)	n=22	n=25			
VAS	0.23 (1.1)	0.36 (1.1)	0.15		
Sound processor use at 6 months	n=22	n=25			
Daily users, n (%)	21 (96)	19 (76)	0.11		

[a] *Only two 6-mm abutments were used, one in the modified MIPS group and one in the original MIPS group.*

[b] *All visits including unplanned visits.*

PART III

Clinical challenges



CHAPTER 6

Clinical presentation, management and outcomes of idiopathic pain in percutaneous bone-anchored hearing implants

Coosje J.I. Caspers
Rik C. Nelissen
Luc M. Verhamme
Frederick J.A. Meijer
Emmanuel A.M. Mylanus
Myrthe K.S. Hol

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Abstract

Objective

To identify clinical features and investigate treatment outcomes of patients with idiopathic pain related to a percutaneous bone-anchored hearing implant (BAHI) and to propose management recommendations.

Study design

Retrospective chart analysis.

Setting

Tertiary referral center.

Patients

The clinical data of 14 patients who were treated for idiopathic pain around their percutaneous BAHI between May 2007 and February 2018 at our tertiary referral center were reviewed.

Main outcome measures

Pain after treatment and implant loss.

Results

All 14 patients received treatment with oral antibiotics. Nine patients received oral antibiotic combination therapy for four weeks, where after pain resolved in four. Out of the five other patients, receiving either antibiotic monotherapy or shortened antibiotic combination therapy, pain resolved in two. In case of persistent pain (57.1%) after initial treatment, other pain management therapies were attempted, however all with only limited effect. Six patients (42.8%) underwent elective removal of the implant. In two patients spontaneous implant loss occurred. In two of the four patients who underwent reimplantation, pain relapsed. In one of these, pain resolved after removal of the new implant. In the other patient, pain persisted, despite abutment removal. With exception of this latter patient, all other 13 patients were pain free at the latest follow-up. Cone Beam CT did not offer additional information regarding diagnosis or treatment.

Conclusion

Idiopathic pain in BAHI is a rare but bothersome symptom which can result in implant removal. After oral antibiotic combination treatment, symptoms resolved in approximately 40% of patients. Therefore, we believe conservative treatment with these antibiotics prior to implant removal surgery, is worth considering.

Introduction

Over the last few decades, the percutaneous bone-anchored hearing implant (BAHI) system has evolved into a well-established hearing rehabilitation that can be applied in a broad spectrum of hearing-impaired patients. Due to several improvements in implant designs (1-3) and surgical techniques (4,5), complications such as adverse skin reactions and implant loss have decreased, especially over the last two decades. These days, the wide-diameter implant (Ø 4.5mm) is the most regularly used implant with a long-term survival rate of 96.2-97.4%. (1,2) Implant loss can be caused by trauma, failure of osseointegration, severe soft-tissue reactions and, in some cases, elective implant removal. According to literature, elective removal is performed in 4.5-7.0% of all implants (6-8) and is conducted because of chronic soft-tissue reactions, recurrent infection, or if other auditory implants are needed due to increased sensorineural hearing loss. (7-9) Another indication for implant removal is persistent pain around the implant which is suggested to be related to skin reactions (9) or occipital neuropathy. (10) However, in most cases no proper explanation for this type of pain is provided. (7,10) Although varying in duration, several cases of idiopathic pain eventually leading to implant loss have been reported. (6,9,11) Based on these literature reports, pain was thought to be a relevant clinical sign in the follow-up of BAHIs and was therefore implemented as a parameter in the newly developed IPS-scale, a soft-tissue assessment scale for percutaneous and transcutaneous implants in which Inflammation (I), Pain (P) and Skin height/numbness (S) are determined. (12)

The etiology of idiopathic pain remains unclear and no diagnostic or treatment strategies have been defined. (7) Defining an adequate therapy is of great importance because idiopathic pain seems to result in a high amount of implant loss. In this study, the clinical data of fourteen patients treated for idiopathic pain related to a BAHI between 2007 and 2018 were retrospectively reviewed. Based on these results, recommendations for therapeutic management are proposed.

Material and methods

All patients who underwent treatment for idiopathic pain related to their percutaneous BAHI at our tertiary referral center between May 2007 and February 2018 were included. This time-interval was chosen, because cases of idiopathic pain were systematically recorded since 2007. Idiopathic pain was defined as pain at the implant site typically increasing during manipulation (ticking on or tightening) of the abutment. Increasing pain suggested that pain was indeed related to the BAHI. Patients were included independent of pain duration. Patients were excluded when a probable cause for the pain, such as an adverse skin reaction (Holgers ≥ 2), was found during clinical examination. The medical records of all included patients were reviewed to obtain the following clinical data: demographic information, medical history, details regarding BAHI implantation and

postoperative complications, symptoms as well as clinical examination at diagnosis and during follow-up, diagnostic and treatment details, removal surgery and total follow-up period.

Current treatment

At our institution, clinicians were advised to initially treat idiopathic pain around a BAHI with oral antibiotics, preferably a combination of Ciprofloxacin 500mg twice daily for two weeks and Clindamycin 300mg three times a day for four weeks (adult dosage). The rationale behind this treatment was that the pain might have been caused by an inflammation of the deeper soft-tissue layers and/or bone around the implant, which was not visible on the outside. Because of the good oral availability and excellent bone penetration of both agents, the above mentioned antibiotic regimen was determined in consultation with the microbiologist. This treatment was advocated independent of duration of pain, in order to prevent further spread of possible inflammation. In case of persisting pain after antibiotic treatment, the following treatment options were available: extending/repeating antibiotics, removal of the abutment and/or implant or, in case of suspected occipital neuralgia, consultation of our institution's specialized pain management team. This pain management team either prescribed oral analgesics or conducted a diagnostic anesthetic block in the region of most intense pain. (10,13) When pain relief was obtained, pulsed radiofrequency treatment of the occipital and/or C2 nerve was performed. The choice for a certain treatment was individually determined by the ENT-specialist based on the effect of oral antibiotics, the severity and duration of complaints, the clinical benefit of the BAHI and the patient's preference. In most patients, a Cone Beam CT-scan (CBCT) was performed in order to detect signs of bone resorption around the implant. (14,15) To evaluate the usability and utility of CBCT in BAHI patients with idiopathic pain, scans were assessed by an ENT-surgeon, radiologist and technician specialized in implantology and 3D technologies.

Statistical analysis

Clinical features were reported as frequencies (%), means (SD) in case of normally distributed data and as medians with Interquartile Range (IQR) in case of not-normally distributed data. With the Chi-square test, associations between clinical variables and the effect of antibiotics were assessed. Data analysis was carried out using SPSS software version 25.0. The level of significance was defined as a P-value of ≤ 0.05 utilizing a Confidence Interval (CI) of 95%.

Ethical consideration

Ethical approval for conducting this study was obtained from the local ethical committee.

Results

Clinical parameters

Between May 2007 and May 2018, 14 patients were identified (table 1). The study population consisted of two men and twelve women with a median age at implantation of 45 years (figure 1A). Four patients (28.6%) were implanted bilaterally yet experienced pain only unilaterally. None of the patients had a history of diabetes mellitus, skin disease or radiation of the skull. Implantation was performed between 1995 and 2014. Since the wide-diameter implant only became available in 2010, most patients had a previous generation implant. Eleven patients were implanted in our tertiary referral hospital and three were referred to us by secondary centers. The 11 patients implanted at our tertiary referral hospital accounted for 1.2% of all 933 patients implanted with a BAHI in our center within this time period. Intraoperative and postoperative complications were assessed for all 14 patients. Exposure of the sigmoid sinus was described in two patients and exposition of the dura mater in one patient. The following postoperative complications were observed: hematoma in one patient and persisting wound dehiscence in two patients. The wound dehiscence lasted for approximately five weeks in one patient, in the other patient time to healing was not documented.

Diagnosis

The time-interval from implantation until onset of pain varied from directly postoperative to 7 years after implantation, with a median duration of 3.2 years. The patient who suffered from a wound dehiscence for an unknown duration developed pain three months after implantation. In the other two patients with a postoperative complication, onset of pain was reported years after implantation. After onset of pain, median time until diagnosis was 19 days (IQR 10 days - 3 months, figure 1B). The type of pain was either characterized as pain around the implant (twelve patients) or as a deep pain below the implant (two patients), whereby pain in all patients increased during abutment manipulation. At diagnosis, no signs of inflammation were present: Holgers 0 (no skin reaction) was observed in 64.3% and Holgers 1 (redness with slight swelling) in 28.6%. However, when looking at medical history, five patients (36%) received treatment for a BAHI-related infection (i.e. Holgers ≥2) within one month before idiopathic pain was diagnosed. Although the infection was successfully treated (defined as Holgers ≤ 1), pain persisted and was therefore considered idiopathic. Three other patients had suffered from recurrent adverse skin reactions in the past, with the last reported episode eight to twelve months prior to onset of pain. In the remaining six patients (43%) no reports of skin problems were found. At the first visit to our clinic after onset of pain, increased skin height was observed in one patient and the presence of sebaceous glands in two patients. In two other patients, a loose abutment was detected and successfully tightened as part of standard care. A loose implant was reported in another patient. In this case, elective removal of the implant was scheduled.

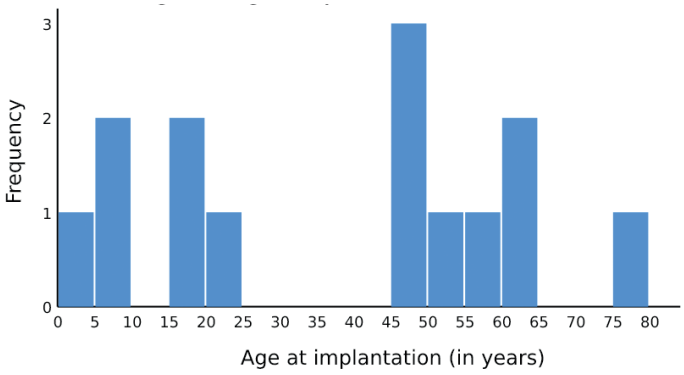
Table 1. Clinical parameters of 14 patients with a bone-anchored hearing implant and idiopathic pain around the abutment

Clinical parameter	Frequency (%)
Gender	
Male	2 (13.3)
Female	12 (85.7)
Age at diagnosis in years, median (range)	45 (5-75)
Implant side	
Right	6 (42.9)
Left	4 (28.6)
Bilateral	4 (28.6)
Implant type	
Previous generation implant	11 (78.6)
Wide-diameter implant	3 (21.4)
Surgical technique [a]	
Dermatoma technique	1 (7.1)
Linear incision with soft tissue reduction	11 (78.6)
Linear incision with soft tissue preservation	1 (7.1)
Implant loss	
No	6 (42.9)
Elective removal without reimplantation	3 (21.4)
Elective removal with reimplantation	3 (21.4)
Spontaneous implant loss and reimplantation	2 (14.3)
Patients with persistent pain at latest follow-up	
No	13 (92.9)
Yes	1 (7.1)
Pain-free patients at latest follow-up [b]	
With bone implant in situ	8 (57.1)
Without bone implant in situ	5 (35.7)

[a] *In one patient surgical technique was missing*

[b] *One patient was not pain-free at latest follow-up*

1A



1B

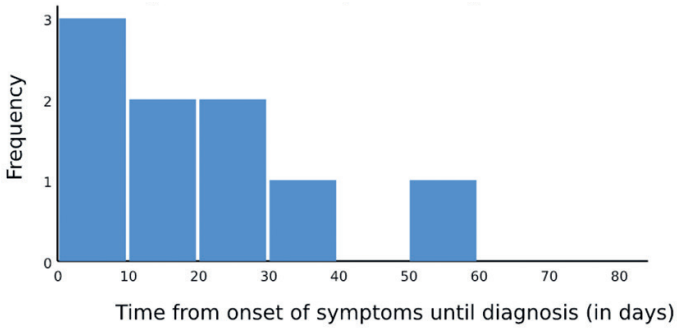


Figure 1. Histogram **1A** showing the distribution of age at diagnosis for all patients (in years). Histogram **1B** presenting the range in time of the duration of pain until diagnosis (in days).

In eleven patients (78.6%) a CBCT was performed. Unfortunately, assessment of these scans showed impaired quality of the implant region due to artifacts caused by implant and abutment (Figure 2). Therefore, a systematic evaluation of these scans was not contributory to this study. Also, no therapeutic or diagnostic management changes were made based on these scans. In one patient, a non-contrast CT-scan was already performed in the referring center. In retrospect, no bone resorption was detected on this scan, however image quality was limited by artifacts. No other imaging techniques such as MRI or ultrasound examination were conducted in this cohort.

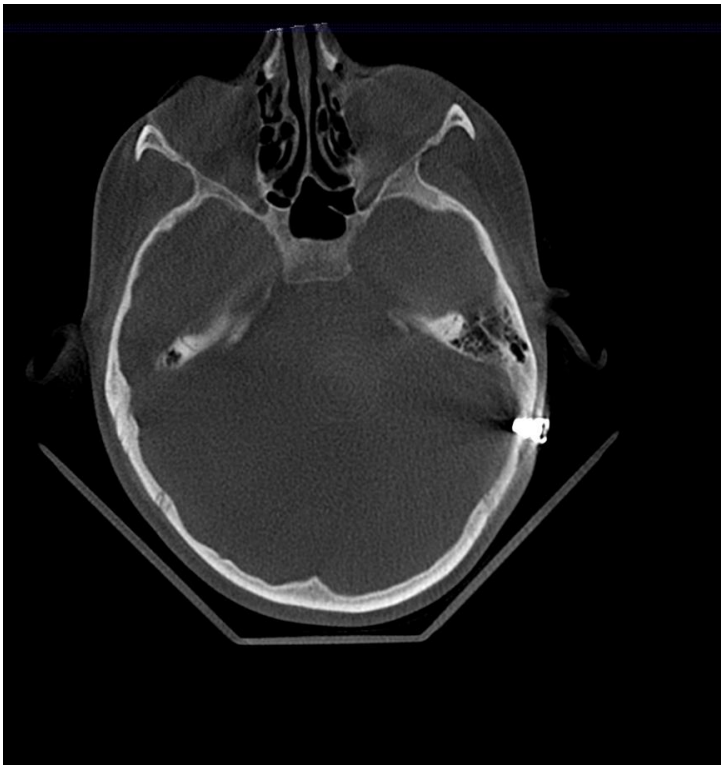


Figure 2. Transversal coupe of Cone Beam CT-scan (CBCT) in a patient with a bone-anchored hearing implant and idiopathic pain.

This CBCT-slice shows artifacts which impair the image quality around the implant. Since image quality was structurally insufficient among all CBCT-scans, (the amount of) bone resorption could not be systematically assessed.

Treatment

All 14 patients were treated with oral antibiotics (figure 3). Prior to antibiotic treatment, local infiltration with an anti-inflammatory glucocorticoid was conducted in two patients with temporary effect. The above mentioned antibiotic combination therapy (ACT) was initiated in ten patients. In one of these patients, abutment change was performed together with the initiation of antibiotics. Four patients received modified antibiotic therapy: in one patient, ACT was shortened because of an allergic reaction to Clindamycin. Another patient was treated with amoxicillin/clavulanic acid prior to ACT. Also, one patient was only treated with Clindamycin monotherapy for six weeks for an unknown reason and the patient with the loose implant screw was treated with Clarithromycin monotherapy for one week awaiting elective implant removal. Out of the nine patients who received ACT only, pain resolved permanently in four (44%). Pain also resolved in the patient in whom ACT was shortened and in the patient in whom abutment change was performed simultaneously. Pain persisted in five patients who received ACT only and in the three

patients who were treated with monotherapy. Among the patients in whom pain resolved after ACT only, median time between implantation and treatment was 3.2 years (range 1.4 months – 7 years) and median time between onset of pain and treatment was 18.5 days (range 0 – 30 days). One of these patients was recently treated for an infection around the BAHI. At follow-up, pain persisted in absence of signs of infection and therefore treatment with ACT was directly initiated. For patients in whom pain persisted after ACT only, median time between implantation and treatment was 4.6 years (range 2.1 months – 8.7 years) and median duration between symptoms and treatment was 29 days (range 4 days – 8.7 years). In this group, three patients had recently been treated for an infection.

In case of persistent pain after initial antibiotics, ACT was extended/repeated (total treatment 8-12 weeks) in four patients and initiated in the patient who received amoxicillin/clavulanic acid. In the latter patient, ACT was later prolonged because pain persisted. In all five patients who received extended/repeated ACT, pain persisted. Furthermore, abutment removal was performed in two of these patients with persistent pain where after pain resolved in one of them. The specialized pain team was consulted in two patients: one was unsuccessfully treated with oral analgesics and in the other one, a diagnostic block of the occipital and C2 nerve was performed, unfortunately without any effect on pain. Occipital neuralgia could not be identified objectively in these patients.

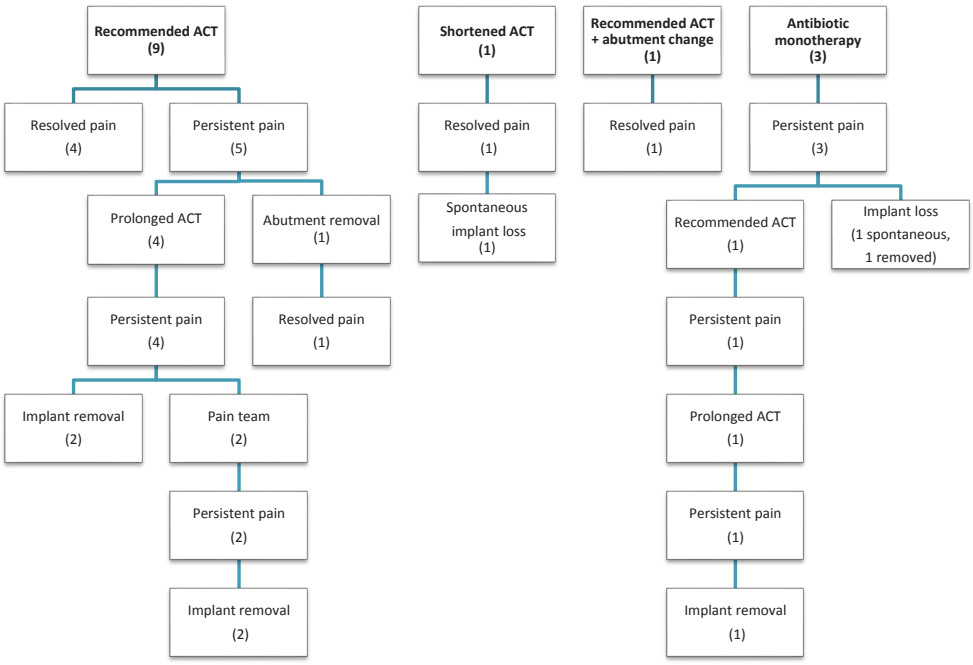


Figure 3. Flow-chart demonstrating the advocated treatment for all 14 patients

ACT indicates antibiotic combination therapy.

Six patients (42.9%) underwent elective implant removal because of persistent pain despite therapy. Two of these patients did not use their sound processor anymore and another two reported decreased usage due to pain. During removal surgery, bone resorption around the implant was observed in one patient. In another patient, exposed dura was found during removal surgery instead of the exposed sinus, which was reported during initial implant surgery. After implant removal, a new implant was inserted in three patients, at approximately five millimeter distance of the removed implant. Three patients did not want a new implant. Two of them could also opt for a conventional CROS device since they suffered from single-sided deafness. The other patient had unilateral acquired conductive hearing loss and did not want a new implant out of fear of a relapse of pain after reimplantation. Spontaneous implant loss occurred in two patients. It occurred in the one patient who was already scheduled for surgical implant removal because of a loose implant screw. This patient was therefore rescheduled for insertion of a new implant. The other implant loss occurred in the patient in whom pain had resolved after shortened ACT. At this moment, this patient is scheduled for reimplantation of a new implant. After implant loss/removal, the implant was examined by the manufacturing company, microbiologist or pathologist in almost all cases. No abnormalities were found, except for one implant which was colonized with the staphylococcus epidermis bacteria.

Follow-up

Median follow-up after diagnosis and removal were 10.51 months (IQR 2.50-32.87) and 7.43 months (IQR 1.15-25.79), respectively. In two out of four patients who underwent reimplantation, pain relapsed. In one of these, pain resolved after removal of the newly inserted implant. In the other patient, pain persisted, despite abutment removal. Implant removal was not scheduled in this patients, since pain was perceived as mild after abutment removal. Except for this latter patient, all other patients were pain-free at the last follow-up.

Discussion

In the last eleven years, 933 patients were inserted with one or two percutaneous BAHI(s) at our center. In 1.2% of these patients, pain without any identifiable cause was reported. In addition, three patients who underwent implantation in other hospitals were referred to our center because of persistent idiopathic pain. Following our local treatment strategy, several treatments were advocated including ACT after which pain initially resolved in 44%. However, not all patients received the recommended therapy and, in the majority of patients, spontaneous implant loss occurred or elective implant removal was performed during follow-up.

Although scarce, some literature is available regarding idiopathic pain in percutaneous BAHI. However, these articles provide limited information regarding patient and treatment characteristics

(6) or merely describe cases of persistent pain which resulted in implant removal. The current study, provides a comprehensive overview of all patients treated for idiopathic pain at a tertiary referral center, including patients in whom pain resolved without implant removal. Badran et al. reported persistent pain in 4.2% of their patients, however no clinical characteristics of these patients were provided. Implant removal due to persistent idiopathic pain was reported in 1.6% of all implants in the study of van der Pouw et al. and in 2.0% of all implants in the studies of Siau et al. and Mylanus et al. Also, the study of Mylanus et al., included implants for auricular epitheses. In line with Siau et al., the majority of patients with idiopathic pain in our cohort were female. This is remarkable since approximately the same number of men and women is implanted with a percutaneous BAHI at our institution. (16) A possible explanation might be the clinical finding that women are more sensitive to pain and are more at risk to develop chronic pain compared to men. (17) Clinical parameters, such as implant type and surgical technique, varied among patients in our cohort. However, since numbers are small, it cannot be concluded that the development of idiopathic pain is independent of these parameters. Time of pain onset in our cohort varied between directly postoperative until years after implantation, which was also observed by Mylanus et al. However, van der Pouw et al. and Siau et al. did not report cases with onset of pain immediately after surgery.

Diagnosis and treatment

Several causes for idiopathic pain have been hypothesized: Faber et al. suggested occipital neuropathy as a probable cause. At our institution, neuropathic pain was not identified objectively in any of the patients. In our cohort, pain relapse after reimplantation was observed in two out of four patients. Because of the small number of patients, no firm conclusions can be drawn from this observation. However, relapse of pain after reimplantation was also noticed by Siau et al. in three out of six patients. Therefore, patient-related factors might be of importance in the development of idiopathic pain. A possible patient-related factor might be hypersensitivity for titanium, which is described in patients with orthopedic and dental implants and might contribute to dental implant loss. (18,19) However, in our cohort no signs of metal hypersensitivity, such as edema or severe redness, were observed.

Another possible explanation for persistent pain could be an inflammation of the deeper soft-tissue layers and bone surrounding the implant, which is invisible on the outside. This hypothesis might be supported by histological studies examining implants removed because of chronic pain. In these studies inflammatory cells were found between the implant and the bony surface. (9,11,20) However, inflammatory cytokine gene expression seems also elevated within the first few months after surgery, and in case of nicotine abuse. (21) In our cohort, 57% of patients suffered from (recent) soft-tissue infections prior to onset of pain. In these patients, bacteria might have migrated along the implant itself into deeper soft tissue layers and bone surrounding the implant. In dental implants a similar peri-implant disease is observed. This disease is called peri-implantitis and is characterized by a deep inflammation around the implant with progressive bone loss. (22) Typical

symptoms include bleeding on probing, swelling and redness. In contrary to the patients in our cohort, pain is only reported sporadically in relation to dental peri-implantitis. (23,24) In our cohort, spontaneous implant loss occurred in two patients, and after ACT pain resolved in 44%. On top of that, non-antibiotic treatments such as oral analgesics, local infiltration with anti-inflammatory glucocorticoids and anesthetic blocks of the occipital nerve did not resolve pain in our and other studies. (7,9) Therefore, a certain manifestation of peri-implantitis might be a possible explanation for patients with persistent pain. However, this raises the question why pain did not resolve in all patients (with a recent infection) after ACT. There might either be another etiology, or the bacteria were insensitive or resistant to the applied antibiotics. Since dental peri-implantitis may result in implant failure and further progression of bone loss, dental literature states the importance of early detection of dental peri-implantitis by radiographic imaging, preferably by intraoral radiography (IR). (25,26) Since IR is not applicable in the field of BAHI and conventional radiography does not provide enough detail, CBCT was performed in 78.6% of our patients to evaluate bone resorption. CBCT is suggested to be accurate in detecting peri-implant bone defects in dental implants (14) and is considered to be a safe diagnostic tool with low patient burden because of the low costs, short scanning time and low radiation exposure. (27) Unfortunately, these scans were not accurately enough to assess bone resorption in our cohort of BAHI patients since artifacts limited the image quality. Although in one study, metal artifacts were only observed sporadically in CBCT (14), most studies reported impaired image quality due to artifacts and therefore limited value of CBCT. (15,25) At this moment, CBCT is not considered a helpful tool in guiding management of BAHI patients with idiopathic pain. More research should be conducted on artifact-reducing techniques, before implementing CBCT as a standard diagnostic tool in assessing bone resorption around BAHI. Another option for assessment of bone resorption might be a CT-scan with Single-Energy Metal Artifact Reduction, which is already shown to improve image quality in patients with aortic stents (28) and coiled intracranial aneurysms. (29) With a contrast-enhanced CT-scan the presence of soft-tissue inflammation or an abscess can also be detected.

At our institution, 65% of patients were initially treated with ACT where after pain resolved in 44% of these patients. The other patients received a modified antibiotic therapy with limited effect. Pain did not resolve in any of the patients who received prolonged ACT. Therefore, it could be suggested that repeating or extending antibiotic treatment might not be efficient. However, given the small number of patients and the retrospective nature of our study, this hypothesis is debatable. It is also possible that pain resolved because of a placebo-effect or because the pain was caused by a self-limiting disease. Unfortunately, a randomized controlled trial is not achievable given the rare manifestation of idiopathic pain in BAHI patients. Since no other effective treatment options are available and oral antibiotics is a non-invasive treatment with low patient burden, we suggest to prescribe ACT prior to implant removal. Especially since many patients (specifically those with a conventional indication) have no other option for hearing revalidation. In patients with no improvement following four weeks of antibiotic therapy, additional antibiotics were not helpful,

and are therefore not recommended. In case of persistent pain despite oral antibiotics, implant removal is the final option. However, beware that pain might relapse following reimplantation. During the preoperative work-up for initial BAHI implantation, patients should be informed about the possible short-term and postoperative complications, including the (small) chance of developing idiopathic pain. Thereby, patients are able to make an informed decision. Not in the least, during follow-up visits after implantation, the presence of pain should be evaluated, for which the IPS-scale seems an appropriate tool.

Conclusion

Idiopathic pain related to BAHI is a rare but inconvenient symptom occurring any time after surgery. Upon today, no clear diagnostic nor treatment strategies have been defined. The lack of adequate treatment options often leads to elective implant removal or implant loss. After oral antibiotic combination treatment, symptoms resolved in approximately 40% of patients. Therefore, conservative treatment with oral antibiotic combination therapy should be considered prior to implant removal surgery, especially in patients for whom no alternative hearing rehabilitation options are available.

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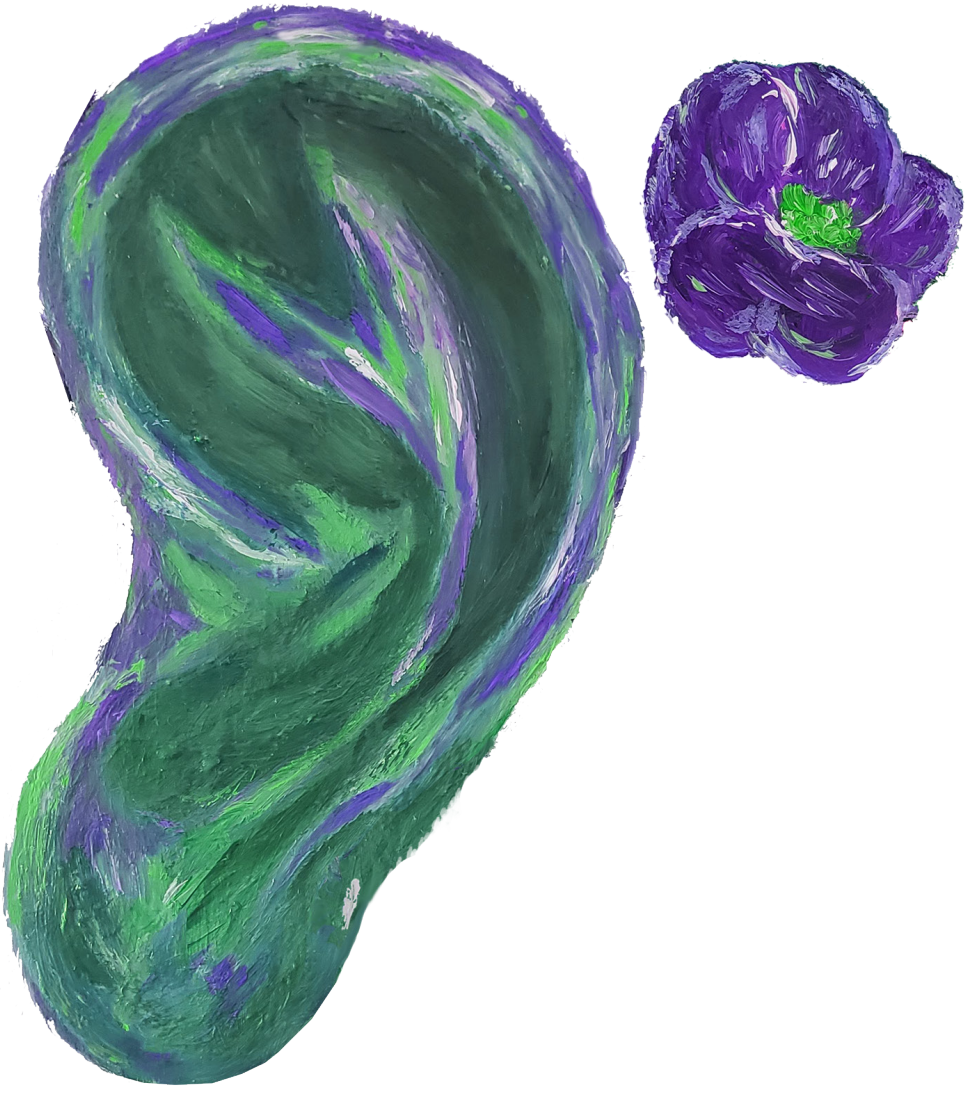

CHAPTER 7

Sound localization with bilateral bone conduction devices

Coosje J.I. Caspers
Arno M. Janssen
Martijn J.H. Agterberg
Cor W.R.J. Cremers
Myrthe K.S. Hol
Arjan J. Bosman

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Abstract

Purpose

To investigate sound localization in patients bilaterally fitted with bone conduction devices (BCDs). Additionally, clinically applicable methods to improve localization accuracy were explored.

Methods

Fifteen adults with bilaterally fitted percutaneous BCDs were included. At baseline, sound localization, (un)aided pure-tone thresholds, sound processor use, speech, spatial and qualities of hearing scale (SSQ) and York hearing-related quality of life (YHRQL) questionnaire were measured. Settings to optimize sound localizing were added to the BCDs. At one month, sound localization was assessed again and localization was practiced with a series of sounds with visual feedback. At three months localization performance, sound processor use and questionnaire scores were determined again.

Results

At baseline, one patient with congenital hearing loss demonstrated near excellent localization performance and four other patients (three with congenital hearing loss) localized sounds (quite) accurately. Seven patients with acquired hearing loss were able to lateralize sounds, i.e. identify whether sounds were coming from the left or right side, but could not localize sounds accurately. Three patients (one with congenital hearing loss) could not even lateralize sounds correctly. SSQ scores were significantly higher at three months. Localization performance, sound processor use and YHRQL scores were not significantly different between visits.

Conclusion

In this study, the majority of experienced bilateral BCD users could lateralize sounds and one third was able to localize sounds (quite) accurately. The localization performance was robust and stable over time. Although SSQ scores were increased at the last visit, optimizing sound processor settings and a short practice session did not improve sound localization.

Introduction

The percutaneous bone conduction device (BCD) is an established hearing rehabilitation method for patients with conductive or mixed hearing loss, if hearing cannot be optimized by surgery or conventional hearing aids. (1) The effectiveness of bilateral BCDs has been questioned, as due to the small intracranial attenuation one BCD will stimulate both cochleas almost equally (2,3). However, already in 1991, Hamann et al. demonstrated the audiological benefit of a second BCD in patients with bilateral conductive hearing loss (BCHL). (4) Subsequently, in 1995, bilateral application of BCDs was gradually introduced. (5) Since then, several studies have shown that bilateral usage of BCDs is effective in improving speech understanding in noise (6-9), hearing-related quality of life (10-12) and sound localization in patients with BCHL (2,6,8,9,11,13-15). In many instances however, patients with BCHL are still unilaterally implanted. (16,17) Sound localization is defined as the ability to identify the direction of a sound source. (18) Sound localization is of major importance to function well in everyday life, for example in traffic or in a crowded environment. Little is known about the actual localization performance in bilaterally aided patients. (8,9,14) Previous studies investigating localization in patients with BCHL used different set-ups and a limited number of loudspeakers. (2,6,8,9,11,14) These studies either investigated whether a patient was able to lateralize sounds, i.e. identify whether sounds were coming from the left or right side (6), or evaluated whether a patient was able to localize sounds correctly within 30^0 or 45^0. (2,8,9,11,14) In the two studies evaluating localization accuracy within 30^0, 50-70% of the patients were able to localize sounds correctly. (8,9) However, with localization accuracy being determined with 7 to 12 loudspeakers at 30^0 angles, it is unclear whether this behavior reflects localization or only lateralization. In a recently published study, a more precise sound localization test with 24 loudspeakers was used to assess localization accuracy in children with BCHL and two BCDs. (11) In that particular study one child with acquired BCHL showed near normal localization behavior, whereas all other children were only able to lateralize sounds. (13) The one child demonstrating near normal localization, indicates that, in principle, it should be possible to localize sounds when fitted with bilateral BCDs. It would be interesting to investigate whether more (bilateral) BCD users are capable of localizing sounds, and to determine the variability in localization behavior between (experienced) users. With sound localization being such an important feature in everyday life (19), it would be of interest to explore whether we can incorporate sound localization improving methods into our clinical practice. Improved localization might be achieved by changes in sound processor settings and by providing localization training. However, with conventional hearing aids, it has been demonstrated that features such as compression and microphone directionality have an effect on localization performance. (20,21) It is still unclear whether this also holds for BCDs. Furthermore, a recent study with normal hearing patients showed that localization training with visual feedback improved horizontal localization accuracy. (22) A similar training in acute monaurally deprived patients also resulted in enhanced horizontal localization. (23)

The current study evaluated sound localization performance in 15 experienced bilateral BCD users, including patients with bilateral congenital and acquired hearing loss. In addition, we explored whether localization could be improved through optimizing sound processor settings and a short localization practice session with visual feedback.

Methods

Ethical considerations

This study was approved by the local ethics committee and was conducted according to ISO14155:2011, the Good Clinical Practice guideline and the ethical principles stated by the Declaration of Helsinki. (24) Written informed consent was acquired from all patients prior to inclusion.

Study population

Fifteen adults with bilateral conductive or mixed hearing loss fitted with two identical sound processors (Cochlear™ BAHA® 4 or 5) were included. Since we aimed to determine the variability in sound localization performance in our patient population, both patients with acquired and congenital hearing loss were included, as well as patients with a slight asymmetry in bone conduction (BC) thresholds. Exclusion criteria were 1) sound processor use less than 5 days a week, 2) less than six months experience with bilateral BCDs and 3) inability to participate in all measurements. The patient inclusion procedure is shown in figure 1. Fourteen patients completed all visits and one patient completed only the first visit. Table 1 presents the characteristics of all patients. Two patients (P3 and P11) had also participated in a previously conducted study on sound localization. (13) Eleven patients had symmetric BC thresholds with an average difference at 0.5, 1, 2 and 3 kHz (PTA4) within 10 dB and individual threshold differences within 15 dB for right and left side. Asymmetric BC thresholds were found in four patients with an asymmetry in PTA4 between 11 and 13 dB (P5, P13, P15) and an asymmetry on individual frequencies between 20 to 35 dB (P5, P12, P13, P15). At the start of the study, the patients had used their bilaterally implanted BCDs for 10.4 years, on average, (standard deviation (SD) 5.3) and all patients had at least one month experience with their current sound processors.

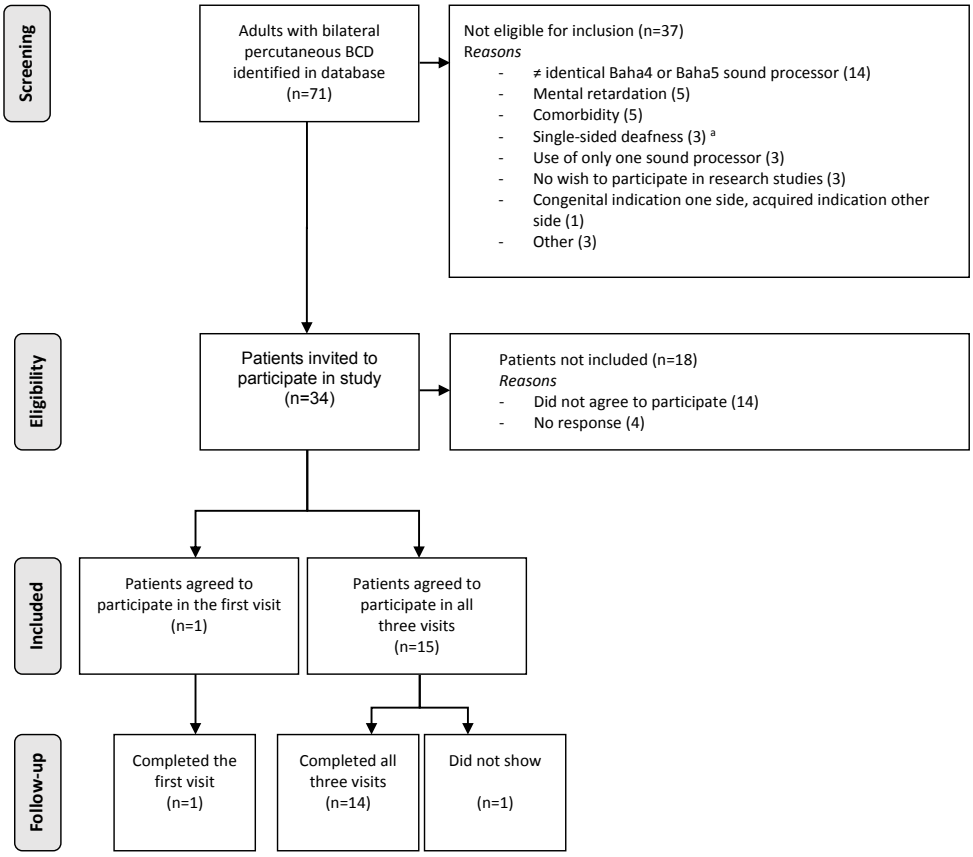

Figure 1. Flowchart of patient inclusion. *BCD indicates bone conduction device.*

[a] These patients were fitted with bilateral BCDs because of single-sided deafness on one side and conductive hearing loss on the other side.

Table 1. Patient characteristics. Atresia was classified according to Cremers et al (44), middle ear anomaly was classified according to Teunissen and Cremers (45).

CHA indicates conventional hearing aid; COM, chronic otitis media; 5p, 5 power; lat, lateralization; loc, localization; poor, poor performer; PTA, pure-tone average at 0.5-, 1-, 2-, and 3 kHz; AC, air conduction; BC, bone conduction; n/a=not assessed.

Patient	Gender	Age (years)	Hearing rehabilitation prior to BCD implantation	Age hearing rehabilitation (AD/AS)	Pre/post-lingual hearing impairment	Age first BCD implantation (years)	Age second BCD implantation	Duration of bilateral BCD use (years)	Etiology	Sound processor type	Localization behavior at baseline with bilateral BCDs	PTA4 AD AC	PTA4 AD BC	PTA4 AS AC	PTA4 AS BC	PTA4 aided thresholds AD	PTA4 aided thresholds AS
P1	F	60	CHA ADS	18/18	post	50	51	9	COM ADS	5	Lat	79	33	54	28	28	29
P2[a]	F	33	CHA ADS	4/4	pre	14	20	13	Microtia, atresia IIB AD Middle ear anomaly IVB AS	5	Loc	63	16	68	16	n/a	n/a
P3	M	20	B71 headband AS	-/1.6	pre	6	6	13	Atresia IIA ADS	5	Loc	56	0	57	-3	19	16
P4	M	74	CHA AD	31/-	post	63	65	9	COM ADS	5	Poor	71	29	73	25	24	24
P5	M	69	CHA ADS	21/20	post	50	62	8	COM ADS	5	Lat	66	20	81	33	25	24
P6	M	75	CHA ADS	45/45	post	64	69	6	COM ADS	5p	Lat	71	48	76	41	34	31
P7	M	38	CHA ADS	7/7	post	22	25	12	COM ADS	5p	Loc	88	35	70	30	33	29
P8	M	69	CHA ADS	32/32	post	46	47	22	COM ADS	5p	Poor	65	38	48	31	23	24
P9[b]	F	44	B71 headband AD	1/-	pre	21	24	20	Microtia, atresia ADS	4	Poor	64	6	68	14	26	28
P10[c]	F	50	CHA ADS	6/6	pre	42	43	7	Atresia IIA ADS	5p	Loc	55	21	46	29	23	24
P11[d]	M	18	BCD headband	0.2	pre	7	7	12	Microtia, atresia III ADS	5	Loc	53	4	68	4	24	22

P12	F	57	CHA ADS	16/17	post	33	46	11	COM ADS	5p	Lat	88	31	68	29	31	34
P13	F	52	CHA ADS	12/15	pre	44	48	4	COM ADS	5p	Lat	81	43	59	32	30	30
P14	M	59	None	-/-	post	48	54	5	COM ADS	5p	Lat	56	30	90	35	23	21
P15	M	66	CHA ADS	34/34	post	39	61	5	COM ADS	5p	Lat	62	13	58	24	27	28

[a] *P2 underwent autologous ear reconstruction for microtia on the right side at the age of 11 (performed in another institution). An exploratory tympanotomy with malleovestibulopexy on the left side was performed at the age of 16. (46) After these surgeries, conductive hearing loss worsened over time on both sides. BCD implantation was performed because optimal hearing rehabilitation could not be obtained by reconstructive surgery and because of recurrent external otitis as result of the occlusion of the ear canal by the mould.*

[b] *For P9, the classification of the atresia was unknown.*

[c] *P10 underwent reconstructive surgery of the external auditory canal on the left side at the age of 3 and 22, and on the right side at the age of 16 and 19. BCD implantation was performed because optimal hearing rehabilitation could not be obtained with conventional hearing aids or surgery.*

[d] *P11 used a BCD on a headband alternating between right and left side.*

Study design

This study consisted of three visits: a baseline visit and two-follow-up visits at one and three months. The aim of the first visit was to determine sound localization performance in 15 experienced bilateral BCD users. The second and third visit aimed to explore whether a change in sound processor settings and/or a short localization practice session would improve sound localization in these patients. The new BCD listening program and the short localization practice were both based on literature reports and on the expert opinion of the authors and designed to be suitable for use in clinical practice.

Baseline measures at the first visit consisted of pure-tone thresholds, sound localization performance, the speech, spatial and qualities of hearing scale (SSQ) (25), the York hearing-related quality of life (YHRQL) questionnaire (26), sound processor use and satisfaction with the BCD. Sound processor use and satisfaction were assessed using the 'daily use of bilateral BAHAs' questionnaire (27) and a visual analogue scale (VAS), respectively. Furthermore, program usage, as logged by the sound processors, was assessed at every visit. Pure-tone thresholds were measured unaided, unilaterally and bilaterally aided. Sound localization was determined in the unilateral aided right, unilateral aided left and bilateral aided conditions. All baseline measures were performed with the patients' habitual BCD settings. At the end of the first visit a second listening program was added to both BCDs with settings to optimize localizing sounds by switching off adaptive microphone directionality and noise reduction, and a linear input-output characteristic by equating low- and high-level gain to the gain for 60-dB input. This fitting strategy was based on previous literature reports which observed a deterioration in localization performance when using adaptive microphone directionality and noise reduction techniques in patients with bilateral conventional hearing aids. (20,21) Furthermore, in our experiences with bilaterally fitting conventional hearing aids, patients preferred linear amplification with a minimum set of sound processing features activated. (28) During the study, only minor gain corrections were applied upon request, while maintaining linear gain settings. Patients were instructed to use this program as much as possible.

After one month, to allow patients to adapt to the new listening program, a second visit was scheduled. During this visit satisfaction with the BCD and sound processor use were determined. Sound localization was again assessed in the bilateral aided condition this time with the new BCD settings. After a short localization practice session, another localization test in the bilateral aided condition was carried out with new settings. Finally, patients were instructed on explicitly using localization cues in daily life. For example, when listening with your eyes closed, guess where the sound was coming from, and subsequently open your eyes. Patients were free to follow up on these instructions as much or little as they wanted, thus mimicking clinical practice.

At three months, the effects of new sound processor settings, practice session, and instructions for daily life were evaluated by measuring sound localization with two BCDs with the settings to

optimize the performance. In addition, the SSQ and YHRQL instruments were filled out and sound processor use was registered. At the end of the study, sound processor settings were set to the patient's preference (i.e. either the original or the new settings).

Localization test and practice session

Sound localization was measured in a sound-isolated anechoic room using the set-up described by Vogt el al. (29) In each session 75 sound stimuli were semi-randomly presented through 24 loudspeakers positioned on an arc between $+70^0$ (right) and -70^0 (left) azimuth and between $+40^0$ (up) and -30^0 (down) elevation. Loudspeakers were shielded by a black, acoustically transparent curtain. Patients were instructed to indicate the location of a sound stimulus by a head movement towards the target. Infrared cameras were used to record these head movements (Smarttrack, ART, Munich, Germany). Determining head movements is known to be an adequate method to assess localization ability. (30,31) The 75 sound stimuli comprised 45 broadband (BB, 0.5-20 kHz), 15 high-pass (HP, 3-20 kHz) and 15 low-pass (LP, 0.5–1.5 kHz) Gaussian noise bursts. The BB stimuli were presented at 45, 55, and 65 dB SPL (15 stimuli at each sound level), whereas all HP and LP stimuli were presented at 55 dB SPL.

The practice session was performed in the same room as the localization test, with eight loudspeakers positioned in the horizontal plane at 21^0 apart. This 30-minute practice session was performed with 65dB SPL BB-stimuli following a stepped approach. As a first step, only six loudspeakers were used and stimuli were presented in a fixed order. Each stimulus was presented twice and the patient was instructed to listen carefully. Then, stimuli were presented randomly and the patient was instructed to indicate the position of the loudspeaker. If all responses were correct, a new task with increased difficulty was presented. In case of an incorrect response, the stimulus was presented again while providing visual feedback on the speaker position. If a patient successfully identified at least four out of the six loudspeakers, the same test was repeated with eight loudspeakers.

Data analysis

Means (SD) and Medians (interquartile range (IQR)) were used to present descriptive statistics. Localization responses were analyzed using the following criteria i) each trial begins with a stable head position between -10^0 and $+10^0$ for at least 100 milliseconds (ms), ii) followed by a head movement starting within 100-1500 ms after stimulus onset, ending with a stable head position, iii) stimuli are perceived within -70^0 (left) and $+70^0$ (right) azimuth. A set of 15 identical stimuli was only included for further analysis, when at least two-third of the responses met these criteria. Data analysis was performed using the approach as described by Vogt et al. (29) Mean absolute error (MAE), response gain (slope), and bias for the best linear fit of the stimulus-response relationship were determined, separately for left and right targets. The MAE is defined as the mean of all the absolute errors, in degrees, between the position of the sound source as indicated by the patient and the actual position of the sound source. Response gain indicates accuracy, with a gain of factor 1 indicating a perfect correlation between target and response. The bias is defined as the offset in degrees. For

a good performer, all data points in the stimulus-response plot will fall along the diagonal resulting in a MAE smaller than 10^0, a gain close to 1 and a bias close to 0. (29,32,33) Individual localization performance was evaluated using the MAE, as well as on visual assessment of the stimulus-response plots by the authors. The Wilcoxon signed rank test was used to analyze localization performance of all patients among the different listening conditions. Changes over time were analyzed with a repeated measures ANOVA (normally distributed data) or Friedman test (not normally distributed data) in case of measurements at three or more time-points, and with the paired T-test in case of measurements at two time-points. For correlation analysis, the Pearson correlation was used.

All analyses were performed using Matlab (MathWorks, Natick USA) and Statistical Package for Social Sciences (IBM SPSS statistics for Windows, Armonk, NY; IBM Corp, Version 25). A confidence interval (CI) of 95% was adopted and p-value of <0.05 was considered statistically significant.

Results

Sound localization

In total 60 out of 435 stimulus sets were excluded because of late responses (P5, P8), stimuli not being perceived (P6, P7, P10, P12, P13) and stimuli being perceived at the back (P4, P6, P9, P15). This mainly concerned 45 dB BB (16 data sets), HP (28 data sets) and LP (8 data sets) stimuli. Localization performance (MAE, gain and bias) with bilateral fitting at baseline did not differ significantly between sound levels or frequency bands. Therefore, localization performance is reported for BB stimuli, pooled for the three sound levels.

Baseline performance

Figure 2 shows the sound localization stimulus-response plots at baseline in the bilateral aided condition with the original sound processor settings for all patients. The MAE and gain values are presented per side. In the bilateral aided condition, localization performance varied considerably among patients. In general, three performance levels were identified: 1) (quite) accurate localization, 2) lateralization only, 3) unable to lateralize sounds. In total, five patients (P2, P3, P7, P10 and P11) were able to localize sounds (quite) accurately. P3 showed near excellent localization performance (MAE$<10^0$) and was considered the best performing patient. P2, P10 and P11 were able to localize sounds to some extent, but not as good as P3 (MAE 14-16^0). P7 was able to localize sounds quite accurately on the right side, but not on the left side. On visual inspection of their stimulus-response plots, we classified P1 and P5 as lateralizers, despite their relatively small MAEs. Including P1 and P5, a total of seven patients were found to be capable of lateralizing sounds (P1, P5, P6, P12-15). The remaining three patients (P4, P8, P9) were poor performers unable to lateralize sounds correctly, although P9 did seem capable of lateralizing sound stimuli which were presented at more than 30^0 off-center.

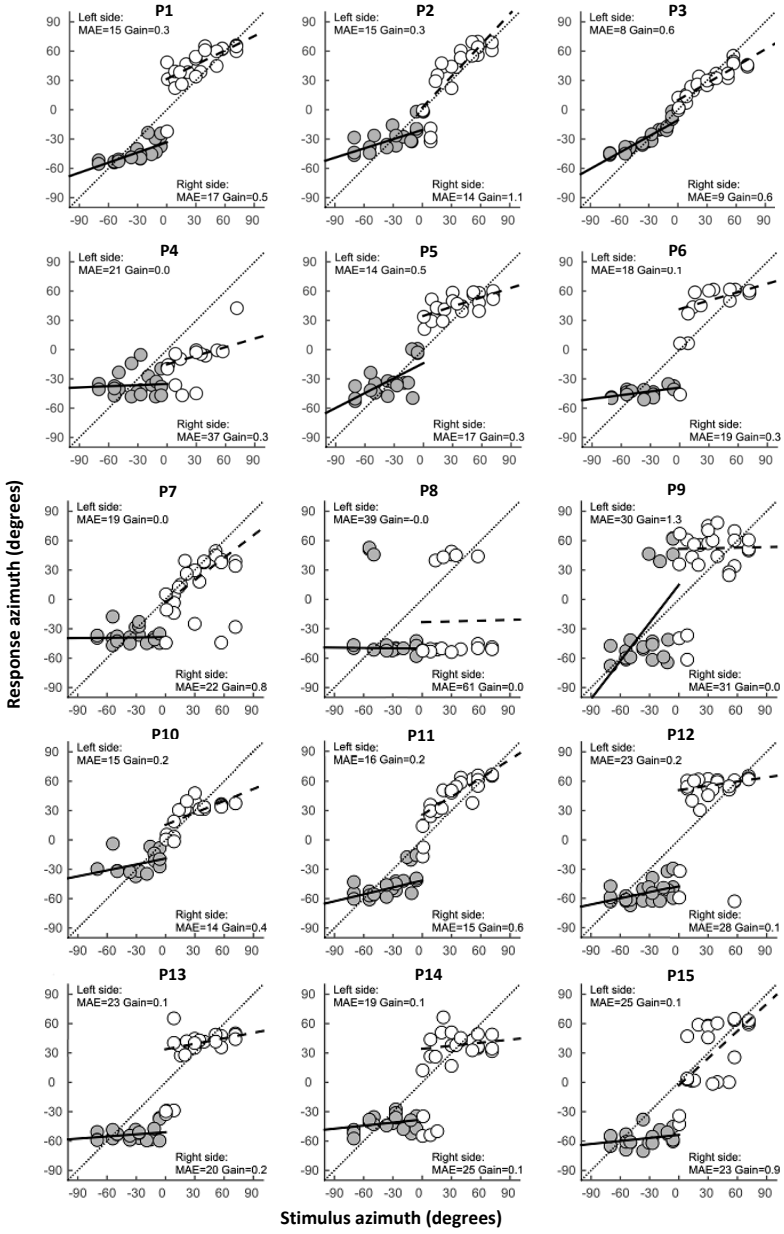

Figure 2. Sound localization stimulus-response plots for all patients in the bilateral aided condition at the first visit with their original sound processor settings.

The target location is plotted on the horizontal axis and the target response on the vertical axis. Negative values represent targets/responses on the patient' left side and positive values represent targets/responses on the patient' right side. Grey circles represent targets on the patient' left side and white circles represent targets on the patient' right side. For a good performer, all data points will fall along the diagonal resulting in a MAE smaller than 10^0 and a gain close to 1. Results are shown for broadband stimuli pooled for the 45, 55, and 65 dB presentation levels in the bilateral aided condition.

Out of the five patients with bilateral congenital hearing loss, four patients (P2, P3, P10, P11) were able to localize sounds (quite) accurately and the remaining patient (P9) was considered a poor performer not capable of lateralizing sounds. Interestingly, localization performance differed per side in P2 and P11. All five patients with a congenital etiology had a symmetric hearing loss with normal (P2, P3, P9, P11) or near normal (P10) BC thresholds. Three of these patients (P3, P9, P11) were rehabilitated with one hearing device on a headband already as a young infant. Bilateral hearing rehabilitation was achieved between the age of 4 and 7 in four patients (P2, P3, P10 and P11) and at the age of 24 in one patient (P9). The patients who were bilaterally rehabilitated during childhood showed (quite) accurate sound localization, whereas the patient P9 in whom bilateral rehabilitation was conducted at the age of 24 was considered a poor performer.

Out of the ten patients with bilateral acquired hearing loss, one patient was able to localize sounds quite accurately (P7), seven patients were capable of lateralizing sounds (P1, P5, P6, P12-15) and two patients were not even able to lateralize sounds (P4, P8) and therefore considered as poor performers. This group of patients with an acquired hearing loss comprised both patients with mild asymmetric BC thresholds and patients with symmetric BC thresholds of 25 dB and worse. BCD implantation was performed sequentially in all patients with an acquired hearing loss with a mean of 7 years (SD 6.6) between first and second implantation. P7 had BC thresholds of 30 and 35 dB and could localize sounds quite accurately on the right side, but not on the left side. The patients capable of lateralizing sounds had BC thresholds ranging from 14 to 43 dB and the poor performers had BC thresholds ranging between 25 and 38 dB. All four patients with asymmetric BC thresholds were capable of lateralizing sounds.

Figure 3 shows the correlation between the MAE in the bilateral aided condition at baseline and aided thresholds, for each side separately. The scatter plots suggest that the MAE, and thus localization performance, deteriorates with poorer aided thresholds. P8, a poor performer, was identified as an outlier and removed from further analysis. Pearson correlation showed a significant positive correlation between MAE and aided thresholds for the left side ($r=0.60$, $p=0.03$), but the correlation for these parameters on the right side was not significant ($r=0.25$, $p=0.42$). The correlation between BC thresholds and MAE was not significant.

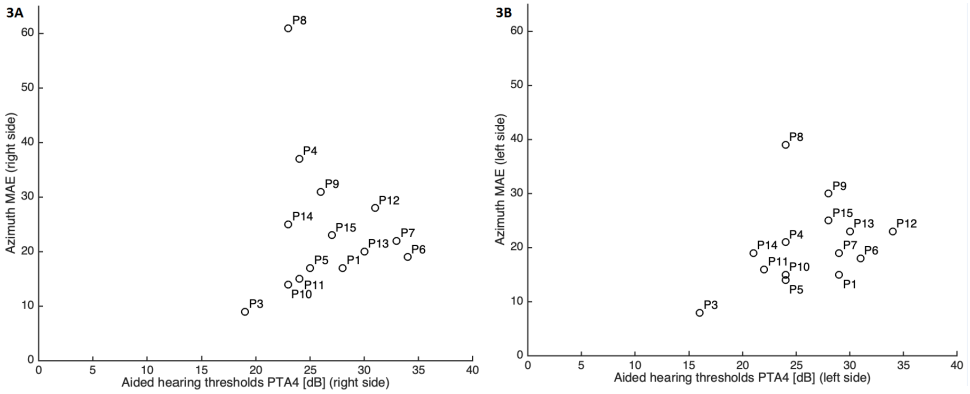

Figure 3. Response azimuth mean absolute error (MAE) for broadband stimuli in the bilateral aided condition at baseline, plotted against the aided PTA4 (mean of 0.5-, 1-, 2- and 3kHz) for right side (**3A**) and left side (**3B**).

P2 is not included in these figures since aided thresholds were not assessed in this patient.

Bilateral versus acute unilateral fitting

With an acute unilateral fitting, patients perceived sounds mainly on the aided side (figure 4). Bilateral fitting significantly improved localization performance compared to the unaided side in the unilateral aided conditions (MAE (Δ median=-58, p=0.000), gain (Δ median=+0.2, p=0.003) and bias (Δ median=-15, p=0.000)), as well as compared to the aided side in the unilateral aided situations (MAE (Δ median=-4, p=0.007), gain (Δ median=+0.2, p=0.000) and bias (Δ median=-14, p=0.000)). P4 was excluded from this analysis due to insufficient reliable data points in the unilateral aided conditions. In P8 bilateral fitting did not improve performance, as stimuli were still mainly perceived on the left side. Interestingly, P8 had slightly worse BC and aided thresholds on the right side, and only perceived 65 dB stimuli while wearing one BCD on the right.

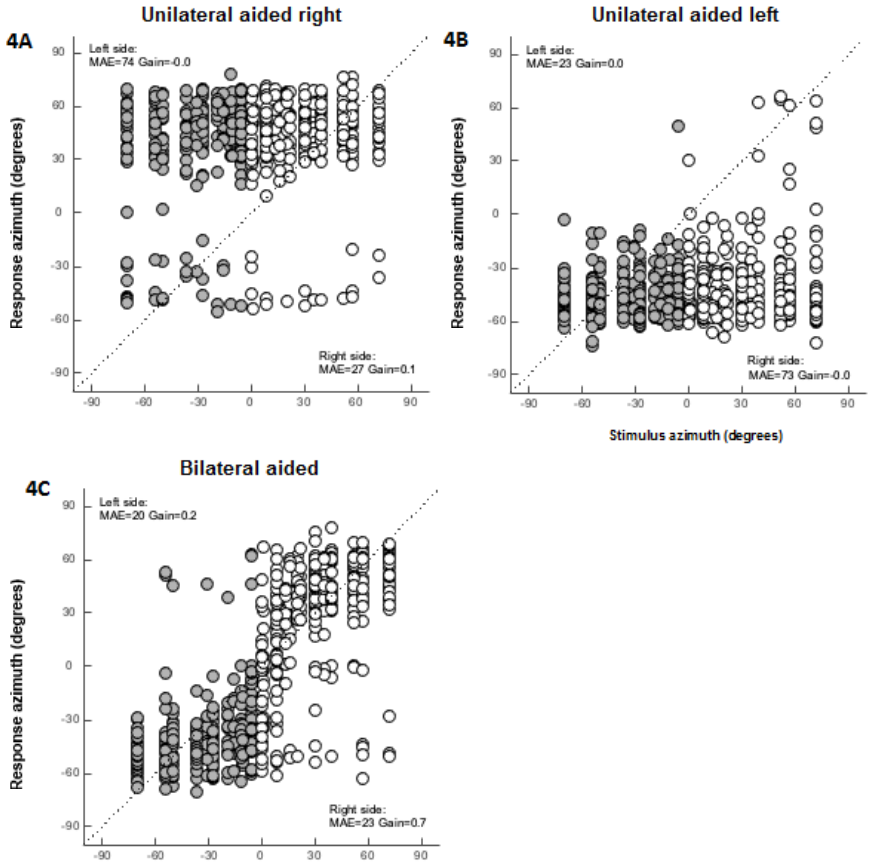

Figure 4. Sound localization stimulus-response plots pooled for all patients in the unilateral aided right (**4A**), unilateral aided left (**4B**) and bilateral aided (**4C**) condition at the first visit.

Grey circles represent targets on the patient' left side and white circles represent targets on the patient' right side. Results are shown for broadband stimuli pooled for the 45, 55 and 65 dB presentation levels.

Localization performance between visits

On a group level, statistical comparisons of the MAE, gain and bias did not reveal any consistent significant differences between visits. In line with this, figure 5 demonstrates that for most patients MAE values were quite similar across the four localization tests in the bilateral aided condition. For a few patients however, MAE values did differ among visits (for instance in P4 and P8, figure 5A). These differences in MAE values were however not consistent over time and differed per side.

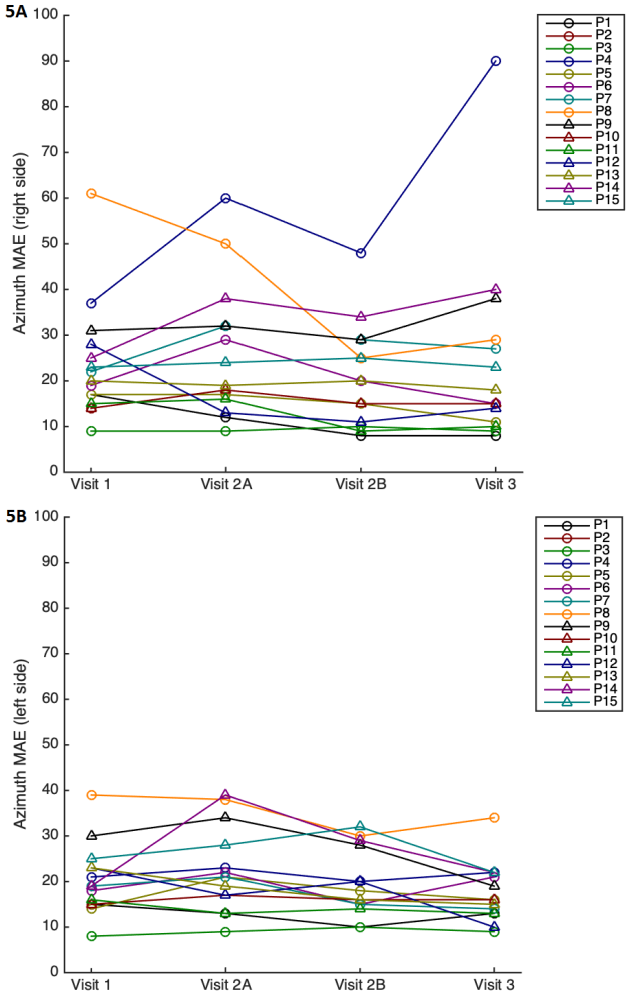

Figure 5. Line graph showing the azimuth mean absolute error (MAE) of broadband stimuli among the four localization tests in the bilateral aided condition, separate for right side (**5A**) and left side (**5B**).

Visit 1 represents baseline measurements, visit 2A the measurement after sound processor settings were changed and visit 2B the measurement after the localization practice session with visual feedback. At visit 3, localization was measured to evaluate the combined effects of sound processor settings and the localization practice session. P2 only participated in the first visit and was therefore not included in these figures.

Sound processor use, satisfaction and hearing-related quality of life

At baseline, all patients reported to be either very satisfied (66.7%) or satisfied (33.3%) with their BCDs with a median VAS of 8.1. All patients used both sound processors simultaneously at all times. Fourteen patients used them more than 12 hours a day and one patient (P8) between 4 and 8 hours a day. Sound processor use or satisfaction with the BCD did not change significantly between visits.

Between the first and second visit, median sound processor use was 15 hours/day (IQR 12-15). The newly added listening program with settings to optimize localization was used most of the time (median percentage of the total wearing time 92%, IQR 80-99%). At the end of the study, 13 patients (87%) preferred the new sound processor settings, specifically because of improved clarity and loudness of sounds. At the third visit, a significant improvement in SSQ scores was found for the subdomains spatial hearing (+1.5, p=0.001) and quality of hearing (+1.0, p=0.006), and for the total score (+0.97, p=0.001). Scores for the SSQ subdomain speech and understanding, and YHRQL did not differ significantly between visits.

Discussion

In this study, the majority of patients with bilateral conductive hearing loss (BCHL) fitted with bilateral bone conduction devices (BCDs) was able to lateralize sounds at baseline (i.e. already during the first visit). Interestingly, bilaterally fitted patients with bilateral acquired as well as patients with bilateral congenital hearing loss, were capable of localizing sounds (quite) accurately. This finding differs from previous research in which localization behavior of both congenital and acquired hearing impaired bilateral BCD users, was limited to lateralization (i.e. localization within 30^0 of the correct speaker location). (8,9) These differences in localization performance might be a result of differences in study design. Whereas in our study the mean absolute error (MAE) was used to describe localization performance, Priwin et al. and Bosman et al. determined correct responses on the precise target location, and correct responses within 30^0 of the target location. (8,9) In the current study, localization performance was thus described more precisely, and to our knowledge this is the first study reporting a robust and stable localization performance (i.e. no variation in performance over time). In the study of den Besten et al. the MAE was also used to determine localization performance with bilateral BCDs. In that particular study all children with bilateral congenital conductive hearing loss were only able to lateralize sounds. (13) The one child able to localize sounds had a bilateral acquired hearing loss. Interestingly, in the current study, both patients with acquired and congenital hearing loss were capable of (fairly) accurate sound localization. Based on the current studied patient population, localization accuracy is not necessarily related to the time of onset of hearing loss. The question remains how to explain the variability in sound localization performance in patients with bilateral BCDs, even within groups of patients with the same etiology. Possible explanations are the variety in age at study participation, bone conduction (BC) thresholds, BC asymmetry and age of bilateral hearing rehabilitation. (34,35) Unfortunately, an extensive statistical exploration of the effect of these characteristics on sound localization could not be performed due to the small sample size of our study population. However, some interesting observations were made.

First of all, sound localization was more accurate in patients with symmetric and near normal bone conduction thresholds when compared to patients with either asymmetric BC thresholds or patients with BC thresholds of 25dB and higher. This might suggest that reasonable localization scores can only be obtained with symmetric, near normal BC thresholds. On the other hand, near normal symmetric thresholds do not warrant good localization performance as one patient with normal, symmetric BC thresholds was not even able to lateralize sounds.

Second, in this study, patients with a limited asymmetry in BC thresholds, were still able to identify whether sounds were coming from the right or left side when using bilateral BCDs. In general, sound localization is known to deteriorate with increasing BC asymmetry. (36) However, little information on exact localization performance in patients with asymmetric bone conduction thresholds and bilateral BCDs is available. Based on the current study, patients with a limited asymmetry seem capable of lateralizing sounds correctly but are not able to localize sounds more precise than that.

Third, two of the patients with congenital hearing loss (P3 and P11) had already participated in another study on localization as a child. In that study with a similar test set-up, the MAEs with bilateral BCDs were 45 (P10) and 36 (P9) respectively (13). In the current study, MAEs of 9 (P3) and 16 (P11) were found for the worst performing side of these patients. The improved MAEs in the current study might be explained by increased experience with bilateral BCDs, by an increasing age or by differences in measurement protocols.

Finally, our findings suggest that a period of hearing rehabilitation with one BCD in patients with bilateral congenital conductive hearing loss does not necessarily rule out fairly accurate localization scores with bilateral fitting in early and middle adulthood. (9) Yet, to achieve this fairly accurate localization ability, bilateral hearing rehabilitation should probably be realized before late childhood, since the main developments in auditor discrimination in normal hearing children take place between 6 to 7, and 8 to 9 years old. (37) Unfortunately, it is not possible to define a precise age cut-off point for bilateral rehabilitation, since it is still unclear at what age spatial processing abilities are fully developed. The development of more specific skills, such as discrimination of stimulus frequency, intensity and duration is thought to continue past this age range. (37,38) Furthermore, maturation of the auditory cortex and growth of the head circumference continue until adolescence and adulthood, respectively. (39,40) Therefore, the four patients in our study who were bilaterally rehabilitated during childhood (i.e. ≤ 8 years of age) might have been able to develop binaural hearing skills within this time window, thus showing (fairly) accurate localization performance.

At our tertiary referral center, bilateral hearing rehabilitation with two BCDs on a softband as early as possible and consecutively simultaneous bilateral percutaneous implantation from the age of 4,

is provided in children with bilateral congenital conductive hearing loss as standard of care since 2009. (27) The rationale behind this practice is the proven benefit of bilateral BCDs in terms of speech understanding in noise (6-9), hearing-related quality of life (10-12) and sound localization in patients with BCHL (2,6,8,9,11,13-15). Furthermore, the current study implies that early bilateral hearing rehabilitation enhances localization skills at a later age. We believe it is of importance to optimize hearing performance as early as possible in order to ensure adequate speech- and language development. Consequently, we recommend bilateral rehabilitation is performed at a subsequent stage, from the age of four. For a future study, it would be interesting to determine sound localization performance in a larger group of adult patients who underwent early bilateral hearing rehabilitation as a child. Such research might confirm the suggested importance of early bilateral revalidation for developing localization abilities.

Improving localization

Even though our customized sound processor settings did not clearly improve localization performance in this study, we would yet suggest to provide this new setting protocol to all bilateral BCD users. The rationale is that the large majority of patients preferred this setting because of its clarity and loudness. A localization practice session suitable for clinical practice was not found to improve sound localization in a group of experienced BCD users. However, scores on the speech, spatial and qualities of hearing scale did improve at the last visit. Our practice session might have been too short to have an effect on localization performance in this group of experienced users. Also, baseline grades for satisfaction with the BCD and sound processor use were already high in this population. This raises the question whether (further) improvement of localization skills is feasible in experienced and satisfied patients. On the other hand, localization training has been effective in other types of hearing-impaired patients (23,41) and not all our patients were capable of localizing sounds. We believe it remains important to further determine factors influencing localization ability, in order to develop efficient methods for improved localization with bilateral BCDs.

Strengths and limitations

This is the first study into evaluating the efficacy of adjusting sound processor settings, and of practicing with visual feedback, on sound localization in patients fitted with bilateral BCDs. Current literature only describes sound processor settings and training in normal hearing patients (22), unilateral hearing-impaired patients (23) or bilateral hearing-impaired patients using conventional hearing aids. (41,42) Therefore, both the listening program with settings to optimize sound localization and the practice session were mainly based on expert opinions. During the localization tests, some patients did not perceive all sound stimuli. Additionally, some patients perceived stimuli at the back, whereas sound stimuli were only presented in the frontal plane. The latter finding is probably a result of front-back confusion due to the absence of pinna cues. (43) For future studies, we would therefore recommend to present broadband sound stimuli of sufficient

intensity within an arc of 360^0. Another possible limitation is that only regular BCD users were included in this study and therefore all patients were (very) satisfied with their BCDs and used both sound on a regular basis. Localization performance of unsatisfied or non-regular users might differ from the findings in our study. Also, localization performance in the unilateral aided conditions represents an acute condition, as all patients were not accustomed to listening with only one sound processor. So, performance in the unilateral aided condition might differ from patients with BCHL who are accustomed to wearing one sound processor.

Conclusion

In patients with bilateral conductive hearing loss, a second bone conduction device (BCD) seems to improve localization performance. The majority of patients fitted with two BCDs could distinguish whether sounds were coming from the left or right side (lateralizing behavior), and one third of patients was able to localize sounds (quite) accurately. All patients with a slightly asymmetric hearing loss were capable of lateralizing sounds. Localization performance was stable over time. Although scores on the speech, spatial and qualities of hearing scale did increase at the last visit, a listening program tailored for localizing sounds and a short localization practice session did not improve localization performance on a group level. More research into the variability in localization performance as well as methods for further improving localization skills in patients with two BCDs is warranted.

Acknowledgements

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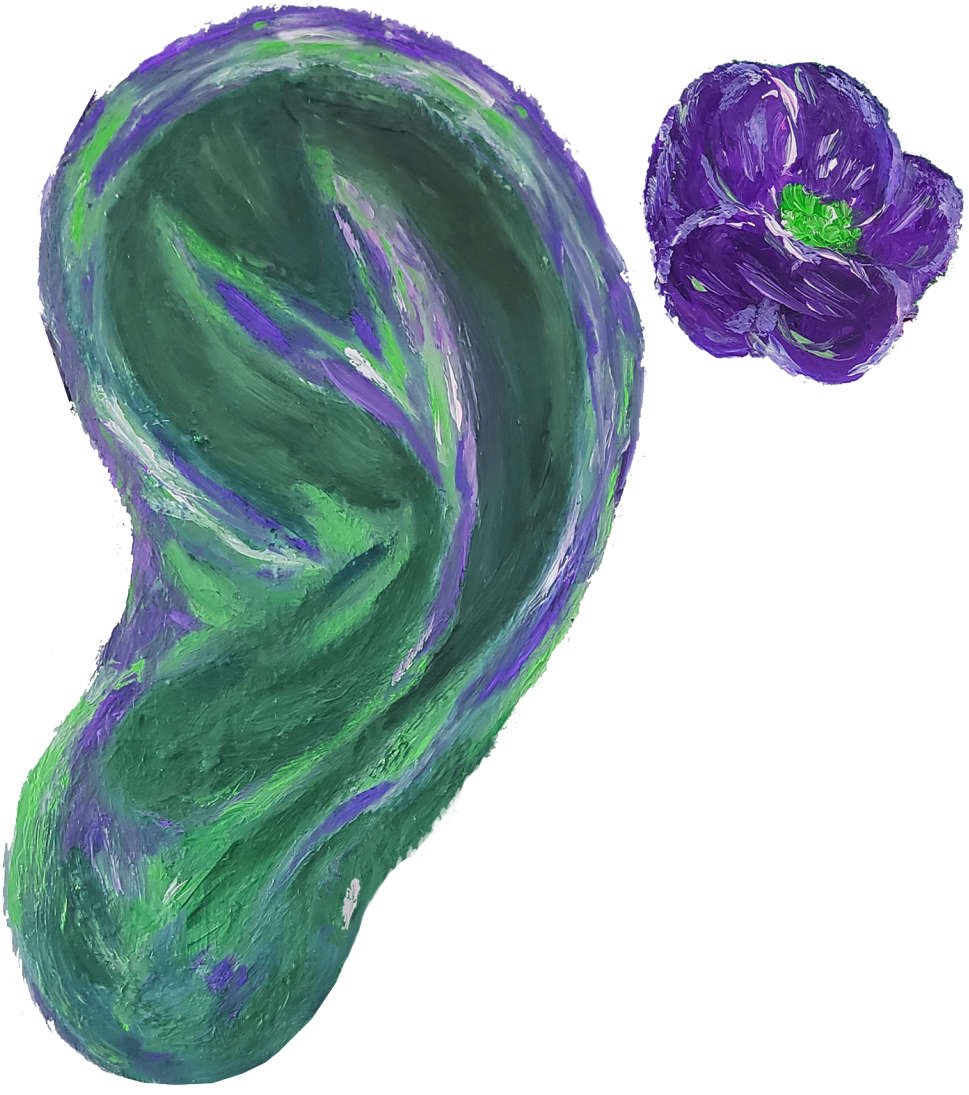

CHAPTER 8

Patient preferences in sound processor loading time after BAHI surgery

Coosje J.I. Caspers and Ivo J. Kruyt
Emmanuel A.M. Mylanus
Rik C. Nelissen
Myrthe K.S. Hol

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Abstract

Objective
Sound processor loading times after bone-anchored hearing implant (BAHI) surgery have gradually decreased over time. This study assessed patient preferences in loading time.

Study design
Prospective patient questionnaire study.

Setting
Tertiary referral center.

Patients
Patients indicated for BAHI surgery received two questionnaires preoperatively: the validated Glasgow Health Status Inventory (GHSI) and a nonvalidated questionnaire that assessed patient preference for loading time and the rationale behind it. This preference questionnaire was also provided immediately, seven days and three weeks (moment of sound processor loading at our center) postoperatively.

Main outcome measures
The preoperative and postoperative preferred loading time and the postoperative changes in preference were determined. Correlations between preference and patient-specific variables were assessed.

Results
Sixty patients were included. Preoperatively, 70% preferred loading within one week after surgery. Of all patients, 43% preferred loading on the day of surgery, mainly motivated by the fast hearing rehabilitation and practical considerations. These preferences were not correlated with the total GHSI score or duration of hearing loss. Directly postoperatively, no change in preference was observed. However, seven days and three weeks after surgery, significantly more patients preferred loading at a later moment. At seven days and at three weeks, 50% and 40% preferred loading within one week, and 12.5% and 7.5% preferred loading on the day of surgery, respectively.

Conclusion
The preference for the timing of sound processor loading varied among patients and differed pre- and postoperatively. Despite the postoperative decline in patients preferring earlier loading, approximately half of all patients preferred sound processor loading within one week after BAHI surgery.

Introduction

Percutaneous osseointegrated titanium bone-anchored hearing implants (BAHIs) have been in clinical use since the 1980s. These systems provide an important hearing rehabilitation option for specific patients with conductive or mixed hearing loss and single-sided deafness. (1-3) There are two stages of implant stability in the temporal bone: primary and secondary stability. Primary stability is defined as the mechanical fixation of the implant in bone directly postoperatively. Secondary or biological stability is achieved through the process of osseointegration. This latter stage involves a dynamic process of bone regeneration and bone remodeling at the bone-implant interface integrating the implant into the remodeled bone. (4) Factors that may influence osseointegration include implant surface characteristics and patient factors, e.g., bone quality and wound healing. (5) Within the first few weeks after implantation, the transition from mechanical stability to biological stability occurs, which may involve a period of reduced stability. (6) Therefore, in the original protocols, implant surgery consisted of two stages allowing a three- to six-month osseointegration time before connecting the percutaneous abutment to the implant. (7) As a consequence, patients had to wait at least three months after initial surgery before they could wear their sound processor. After the introduction of a one-stage surgical approach in adults, it became feasible to decrease sound processor loading times. (8) During a consensus meeting in 2005, a loading time of four to six weeks after implantation was advised for adults. (1) A large retrospective review in 2012 showed that loading the bone conduction device (BCD) on the BAHI three to five weeks postoperatively in healthy adults resulted in similar rates of adverse skin reactions and implant survival compared to longer loading periods. (9) Additionally, since the introduction of the wider diameter implants (Ø 4.5 mm compared to 3.75 mm), loading times of three weeks were found to be safe. (10,11) This wider implant diameter design was developed to increase the implant–bone contact area and, therefore, to improve the initial stability and increase the surface area for osseointegration. Recently, even shorter times until loading have been reported to be sufficient. (12,13)

All currently published studies assessing optimal loading time have merely focused on objective clinical endpoints, such as implant loss, the implant stability quotient (ISQ), and skin complications. However, in light of patient-centered care (14), we believe it is of utmost importance to investigate patients' preferences and perspectives regarding optimal loading time after BAHI surgery, especially since loading after one week has been proposed.(12)

Methods

This single-center, prospective, questionnaire study determined patient preferences for sound processor loading times after BAHI surgery and evaluated the rationale behind it. The current

study also assessed whether patient preferences differed pre- and postoperatively and whether this could be explained by postoperative complaints or other variables.

Study population

Patients aged ≥ 18 years with normal bone quality and those indicated for percutaneous BAHI surgery with a Wide Ponto implant® (Oticon Medical AB, Askim, Sweden) or a Cochlear BI300 implant® (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden) were included. Patients were excluded according to the standard exclusion criteria used in clinical trials conducted at our center, namely: 1) reimplantation surgery, 2) a medical history of disease and/or treatment compromising bone quality at the implant site, e.g., radiation therapy or osteoporosis, 3) mental disability or a medical history of psychiatric disease, and 4) inability to participate in the follow-up. (15-19) The included patients were randomly divided into four groups: groups A, B, C and D. Group A consisted of 30 patients, and groups B, C and D consisted of 10 patients each. All groups received two questionnaires before surgery. Postoperatively, three questionnaires were administered. Group A received these postoperative questionnaires at three previously defined time points: directly after surgery, seven days after surgery and on the day of sound processor loading (approximately three weeks). Groups B, C and D received these postoperative questionnaires at only one out of three postoperative time points: group B received the questionnaires directly postoperatively; group C received the questionnaires seven days postoperatively; and group D received the questionnaires on the day of sound processor loading. This study setup was chosen to detect and, if needed, account for practice bias in the repeatedly sampled group (group A). Practice bias could be induced by assessing the same questionnaires at multiple time points.

All study participants were treated according to our standard clinical care, including sound processor loading approximately three weeks after surgery. To determine baseline values, all included patients (test and control) received two questionnaires before surgery: the validated Glasgow Health Status Inventory (GHSI) (20) and a specific questionnaire inquiring about loading time preferences. The GHSI measures the impact of patient hearing impairment on hearing-related quality of life (HRQoL), resulting in a total score and three subscores (general, social support, and physical health). All scores range between 0 and 100, with a higher score indicating a better HRQoL. The outcomes of the GHSI were used as a measure to determine whether patient preferences in loading timing were influenced by the severity of their hearing impairment. The loading time preference questionnaire is a nonvalidated set of questions in which patients select their preferred moment for sound processor loading. They can choose from six options, ranging from the day of surgery to more than three weeks after surgery. Patients are also asked to specify a reason for selecting this specific moment. The postoperative questionnaires consisted of the loading time preference questionnaire and two visual analogue scales (VAS), which assessed subjective well-being and the severity of complaints after surgery; higher grades on these VAS

scales indicate a better well-being and a higher complaint-severity level, respectively. In addition to the questionnaires, demographic data and patient-related characteristics were collected.

Statistical analysis

Descriptive data were presented as frequencies (%), means (standard deviations (SDs)) and, in cases where data were not normally distributed, medians with interquartile ranges (IQRs). Between-group comparisons were performed using the chi-square test for nominal variables and the Kruskal-Wallis test for continuous and ordinal variables. For the correlation analysis, the Spearman correlation coefficient was used in the case of continuous and ordinal variables, and the Pearson correlation coefficient was used in the case of normally distributed dichotomous variables. For nonnormally distributed dichotomous variables, the Mann-Whitney U test was performed to detect a difference in preference between the two values of the variable. Changes in the preferred loading time were assessed using the Wilcoxon signed rank test. With the independent t-test (normally distributed continuous data), Mann-Whitney U test (not normally distributed continuous data) and Fisher's Exact test (categorical binary data), clinical variables were compared between patients who changed their preferred loading time postoperatively and patients who did not.

All statistical analyses were carried out using SPSS statistics v. 25.0 (IBM Corp., Armonk, NY). A confidence interval (CI) of 95% was utilized, and a p-value < 0.05 was considered statistically significant.

Ethical considerations

This study was approved by the local ethical committee and conducted according to the guidelines established in the Declaration of Helsinki (Washington 2002, ISO 14155) and Good Clinical Practice (International Conference on Harmonization Good Clinical Practice). Upon inclusion, informed consent was obtained from all participants.

Results

A total of 60 patients were included in this study and implanted with a percutaneous wide-diameter BAHI. Table 1 presents the clinical and surgical characteristics of these patients. No major perioperative complications occurred. The demographic characteristics, preoperative duration of hearing loss, GHSI scores and surgical indications did not differ between groups. The median VAS score for well-being directly postoperatively was 10 (IQR 8-10). At seven days after surgery and on the day of loading, the median VAS score for well-being was 9 (IQR 8-10). The median VAS score for the severity of complaints was 0 at all postoperative time points with an IQR of 0-0 directly postoperatively, 0-4.5 seven days after surgery and 0-2 on the day of loading.

Between-group comparisons showed a significantly lower VAS score for well-being on the day of loading for group D compared to group A. Since all other outcome measures were comparable between groups at any time point, further data analyses were performed on the compiled data of all patients.

Table 1. Clinical parameters of all 60 patients

Clinical parameter	Frequency (%)
Gender	
Male	24 (40.0)
Female	36 (60.0)
Age at surgery, mean (SD)	57 (15.0)
Ethnicity	
Caucasian	57 (95.0)
African	1 (1.7)
Asian	2 (3.3)
Smoking	
No	33 (55.0)
Yes	13 (21.7)
Unknown	14 (23.3)
Duration of hearing loss in years, median (IQR)	24 (9-48)
Glasgow Health Status Inventory, mean (SD)	
Total score	54.3 (9.1)
General score	49.2 (11.1)
Social score	83.6 (1.6)
Physical score	44.9 (22.9)
Previous BAHI experience	
Yes [a]	7 (11.6)
Indication	
Acquired conductive hearing loss	45 (75.0)
Congenital conductive hearing loss	2 (3.3)
Single-sided deafness	12 (20.0)
Perceptive hearing loss [b]	1 (1.7)
Surgical technique	
Linear incision technique	36 (60.0)
minimally invasive Ponto surgery	24 (40.0)
Anesthetic technique	
Local anesthesia	50 (83.3)
General and local anesthesia	10 (16.7)

Perioperative complications	
None	47 (78.3)
Drilling into vein	4 (6.7)
Exposed dura	9 (15.0)

[a] *These patients either underwent reimplantation or received a second BAHI.*

[b] *Conventional hearing aids were contraindicated in this patient.*

Preferences in loading time

Table 2 shows the patient preferences in loading time per assessment time point. Preoperatively, the majority of patients (70%) preferred sound processor loading within one week after surgery. Out of all patients, 43% preferred loading on the day of surgery, mainly motivated by the fast hearing rehabilitation and practical considerations (implantation and sound processor loading in one visit instead of two). Patients who did not prefer immediate loading stated that they needed time to heal and/or get accustomed to the implant.

Table 2. Preferences in loading time at the four different time points at which the loading time preference questionnaire was administered.

Time point of questionnaire	Before surgery	Directly after surgery	7 days after surgery	± 3 weeks after surgery
Preference	*n (%)*	*n (%)*	*n (%)*	*n (%)*
0 days	26 (43.3)	14 (35.0)	5 (12.5)	3 (7.5)
1-5 days	6 (10.0)	6 (15.0)	8 (20.0)	7 (17.5)
1 week	10 (16.7)	7 (17.5)	7 (17.5)	6 (15.0)
2 weeks	2 (3.3)	3 (7.5)	6 (15.0)	5 (12.5)
3 weeks	13 (21.7)	10 (25.0)	9 (22.5)	16 (40.0)
> 3 weeks	3 (5.0)	0 (0.0)	5 (12.5)	3 (7.5)
Total	60 (100)	40 (100)	40 (100)	40 (100)

A weak, positive, monotonic correlation between preoperative preference in loading time and the GHSI general score was observed (r_s 0.27, n=60, p<0.037). However, no significant correlations were found between any of the other GHSI (sub)scores and preoperative preferences. Furthermore, the preoperative preference did not correlate with other clinical variables, such as age, preoperative duration of hearing loss or indications. Additionally, no difference in preferred loading time was observed between males and females or between patients with and without BAHI experience.

At the three postoperative time points, the preference for loading on the day of surgery ranged from 7.5% to 35%. Additionally, 22% to 40% of the patients preferred loading three weeks after surgery. For each time point, correlations between preference in loading time and patient-specific variables such as demographic data, surgical technique, perioperative complications and postoperative VAS scores were assessed. A weak, positive, monotonic correlation was observed between age and the preference for loading directly postoperatively (r_s 0.39, n=40, p=0.038). This indicates that younger patients prefer loading at an earlier moment. A weak, positive, monotonic correlation was also found between the grade for severity complaints and preference at seven days after surgery (r_s 0.32, n=40, p<0.045). Additionally, at seven days after surgery and on the day of loading, females preferred loading at a significantly later time point compared to males (U=259, p=0.014 and U=273, p=0.047). No correlations were found between postoperatively preferred loading times and ethnicity, preoperative duration of hearing loss, or indications. Postoperative preferences were not significantly different for patients with BAHI experience, compared to patients without experience. Additionally, similar postoperative preferences were found for patients with and patients without a perioperative complication, as well as for patients who underwent surgery using minimally invasive Ponto surgery and patients who were implanted using the linear incision technique with soft tissue preservation.

Postoperative change in preferred loading time

Figure 1 shows the preferred loading times at the preoperative time point and the three postoperative time points. As illustrated in this figure, comparable preferences for the time of loading were observed preoperatively and directly after surgery. However, at seven days and on the day of loading, the preferred loading time increased significantly compared with the preoperatively preferred loading time (Z=-2.76, p=0.006; Z=-3.55, p<0.001, respectively); at these postoperative time points, only 50% and 40% of the patients preferred loading within one week, respectively. Specifically, the number of patients with a preference for loading on the day of surgery declined.

When assessing postoperative changes in the entire population, 50% of the patients did not change their preference, 40% had a preference for loading at a later time point and 10% had a preference for loading at an earlier time point. Out of the 26 patients with a preoperative preference for loading on the day of surgery, 15 (58%) changed their preference to loading at a later time point postoperatively. Patients changing their preference to loading at an earlier time point, all had a preoperative preference for loading three weeks after surgery.

None of the patients changed their preference for loading on the day of surgery. The patients who preferred loading at a later time point postoperatively stated that more time was needed to recover from surgery, to obtain complete wound healing, or to get accustomed to the implant than was expected beforehand. The VAS score for well-being seven days after surgery was significantly lower in these patients (U=94, p=0.027) compared to patients who did not change their

preference postoperatively. A nonsignificantly lower VAS score for well-being (U=113, p=0.069) and a nonsignificantly higher VAS score (U=116, p=0.063) for the severity of complaints were also observed in this group on the day of loading. In contrast, a few patients preferred loading at an earlier moment because the surgery itself had less impact and because wound healing occurred faster than expected preoperatively.

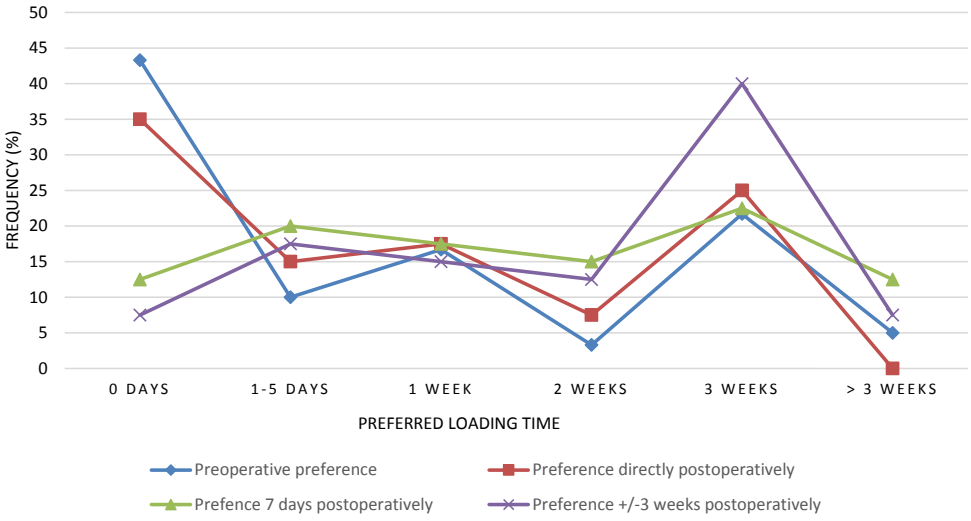

Figure 1. Preferred loading time for the total study population at the preoperative and three postoperative time points.

The blue line represents the preoperative preference, the red line preference directly postoperatively, the green line preference at 7 days after surgery and the purple line preference on the day of loading.

Discussion

At our center, sound processor loading after BAHI surgery is usually performed approximately three weeks after surgery. Currently, earlier loading times have been proposed. (12,13) Since little is known about the effects of patient perspective on the timing of loading, this study aimed to evaluate patient preference regarding the moment of sound processor loading after BAHI surgery. When asked preoperatively and directly postoperatively, the majority of patients preferred loading within one week after surgery. Loading on the day of surgery was preferred by one-third in almost half of all patients. However, at the other postoperative time points (seven days and the loading moment at approximately three weeks), these numbers declined, and significantly more patients preferred sound processor loading at a later point in time compared to their preoperative preferences.

Strength and limitations

To the best of our knowledge, this is the first study to evaluate the effects of patient perspective on the timing of sound processor loading. The major strengths of this questionnaire survey were its prospective nature and relatively large sample size. Furthermore, correlations between patient-specific variables and preferred loading time were determined to detect possible confounders for loading time preferences. However, a few limitations of this study can also be addressed. Upon inclusion, patients were informed about the aim of the study. Study participants were also aware that sound processor loading was usually performed around three weeks in our institution. This might have resulted in a response bias. Furthermore, other variables such as travel distance to the hospital or use of a contralateral hearing aid might also have influenced the preference of our patients and were not assessed. To detect potential practice bias, questionnaires were distributed at multiple postoperative time points in group A and at only one postoperative time point in groups B, C and D. Unfortunately, this setup resulted in some disadvantages in terms of the comparisons over multiple time points. Since both paired and unpaired data were present at each postoperative time point, comparisons of the preferences in loading times could only be conducted for each postoperative time point individually. Finally, nonvalidated questionnaires were used, and the generalizability of this study is arguable since all patients underwent surgery in one tertiary referral center in one country.

Interpretation of the findings

The number of patients preferring an earlier moment for sound processor loading than the current clinical practice at our institution was initially very high but did decline seven days and approximately three weeks after surgery. These patients reported preferring a later moment in time because they needed more time to heal and/or become accustomed to the implant. A significantly lower VAS score for well-being and a nonsignificantly higher VAS score for severity of complaints was also observed in this group. Since the preference directly postoperatively did not differ from the preoperative preference, it might be suggested that most patients were well aware of the impact of the BAHI surgery itself but underestimated the postoperative period. The observed change in loading time preference could, however, also have been caused by response bias. It seems that (some) patients were inclined to choose the same time point for loading as the time point at which they received the questionnaire. When the questionnaire was, for instance, assessed seven days postoperatively, a higher number of patients preferred loading within one week after surgery. When the questionnaire was assessed on the day of loading, an increase in preference for loading at (more than) three weeks was observed. Another possible explanation for the changing preferences is confounding clinical variables. To account for such variables, several patient-specific variables were assessed. One of these variables was previous experience with a BAHI. Interestingly, no differences in preference were observed between patients with and without BAHI experience. In the correlation analysis, only weak correlations, which were not consistent over the different time points, were found. For example, the GHSI general score correlated with preoperative

preference, whereas age correlated with preference directly postoperatively. Additionally, while the severity of complaints was correlated with the preference seven days after surgery, it was not correlated with the preference directly after surgery or at approximately three weeks after surgery. Because of these inconsistencies, it is difficult to interpret these outcomes and to determine which variables truly contribute to the variability in preference for loading time. With caution, it could be hypothesized that patients with a lower GHSI general score have a higher disease burden and therefore prefer earlier loading preoperatively. Postoperatively, other clinical variables, such as well-being and severity of complaints (or other non-assessed clinical characteristics), were more important in the preference for a certain point in time. Since the impact of these variables on loading time preference cannot be estimated preoperatively, it is unfortunately not feasible to include these variables in a standardized loading time scheme.

Implication of these findings

Despite the limitations of this study and the postoperative decline in preference for earlier loading, a relevant number of patients preferred sound processor loading at an earlier moment than currently advocated: loading within the first week after surgery was preferred by 40% and 50% of the patients when asked seven days and approximately three weeks postoperatively, respectively. On the other hand, sound processor loading at (more than) three weeks (the current practice) was preferred by a substantial number of patients as well (35-47.5%). Thus, based on our findings, the preference for the time of sound processor loading varies among patients and differs pre- and postoperatively. Unfortunately, no clear explanation for this variability was found in this study. Currently, the focus on patient-centered health care is increasing, and we believe it is important to provide care that is in accordance with patient preferences. However, it should also be feasible to deliver this care, in terms of safety, logistics and finance. Bearing this in mind, one possible way to cater to our patients' preferences and to improve efficacy could be loading the sound processor one week after surgery. Loading can then be combined with the regular postoperative follow-up visit, resulting in fewer visits. The study conducted by Hogsbro et al. demonstrated that loading at one week is also feasible regarding safety. (12) In this study of 25 patients, no implant losses or decreased ISQ values were observed after sound processor loading at one week postoperatively. We should, however, take into account that only adult patients with normal bone quality were included in this study and that sound processor loading was only performed in cases of sufficient soft tissue healing. The same was applied for the study conducted by Hogsbro et al., in which loading was performed two weeks after surgery. (13) Therefore, it remains questionable whether loading within one or two weeks would be safe in the entire adult patient population. In addition, based on the findings in the current study, not all patients prefer earlier loading. Another option for sound processor loading would be to conduct loading when sufficient stability (based on ISQ values) and wound healing have been reached, as proposed by McLarnon et al. and Mierzwinski et al. (21,22) However, such a protocol might induce logistic challenges and uncertainty for the

patients. Moreover, the correlation between ISQ and osseointegration is still debatable, and no lower limit ISQ value at which loading is safe has been determined. (13,15)

Conclusion

Despite the postoperative decline in patients preferring earlier loading than currently advocated, approximately half of all patients preferred sound processor loading within one week after bone-anchored hearing implant surgery. To both cater to our patients' preferences and improve hospital efficacy, sound processor loading one week (instead of three weeks) after surgery might be implemented. However, when determining the time of sound processor loading, in addition to individual patient preferences, logistics and clinical characteristics should always be taken into account.

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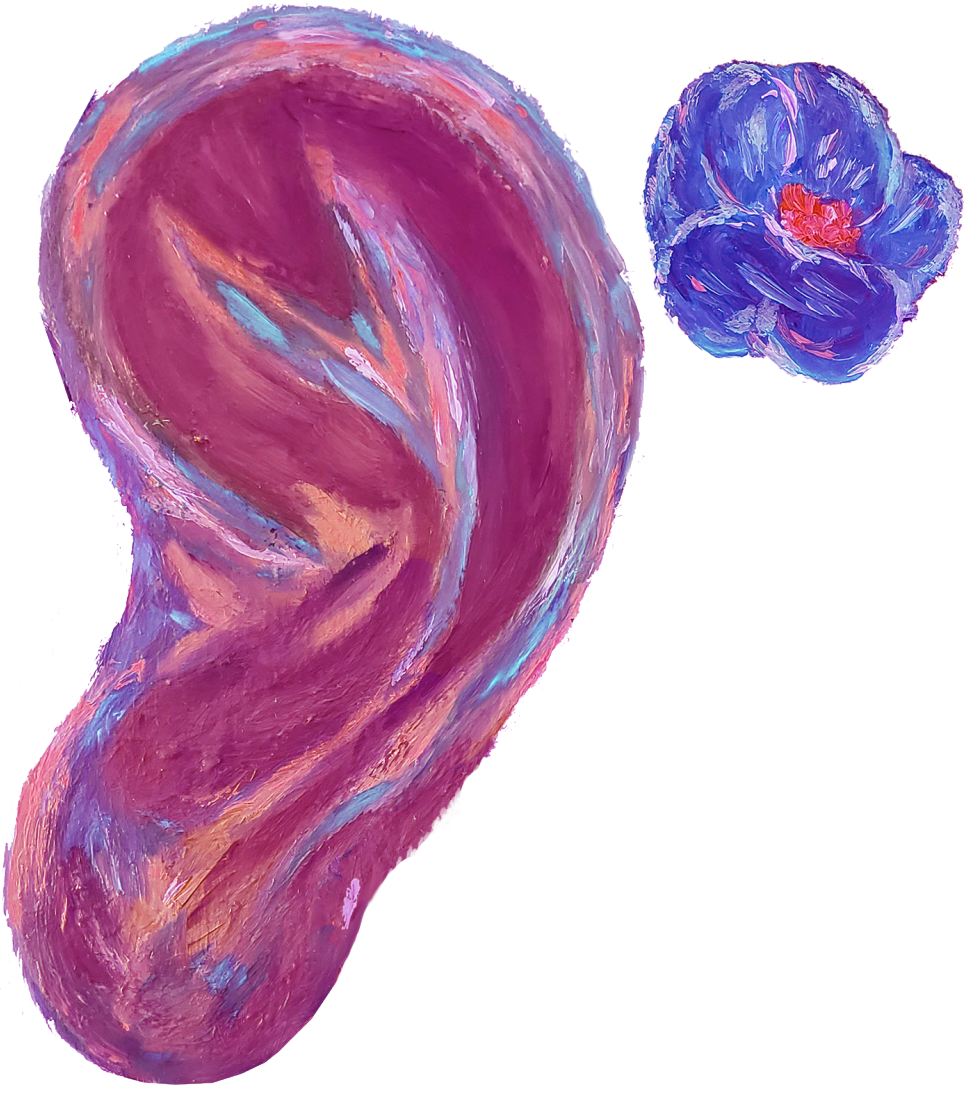
PART IV

General discussion and summaries



CHAPTER 9

General discussion

Since the first implantation of a percutaneous bone-anchored hearing implant (BAHI) in 1977, clinical BAHI research mainly focused on improving postoperative clinical outcomes by introducing new surgical techniques and new implant and abutment designs. This resulted in a shift to minimally invasive techniques and fewer postoperative complications. However, complications still occur and research on further improvement of clinical outcomes is still needed. This thesis provides an overview of postoperative clinical and hearing-related quality of life (HRQoL) outcomes of current surgical procedures and implants (part I), an investigation whether minimally invasive Ponto surgery (MIPS) has added clinical value over the current gold standard surgical procedure (part II), and, in an attempt to further optimize care for individual groups, the exploration of three present-day issues within the BAHI-field (part III). The latter part resulted in a proposed treatment scheme for idiopathic pain, an overview of sound localization performance in patients with bilaterally fitted BAHIs, and an evaluation of preferred sound processor loading times.

Part I: State of the art – clinical outcomes and hearing-related quality of life

The current gold standard BAHI procedure involves implantation of a 4.5-mm-wide implant using the linear incision technique with soft tissue preservation (LIT-TP). **Chapter 2** of this thesis evaluated the five-year postoperative clinical outcomes of this implant type and surgical procedure and compared these to the outcomes of the previous generation 3.75-mm-wide implant and the linear incision technique with soft tissue reduction (LIT-TR), respectively. Because of its increased bone-implant contact area, it was hypothesized that the 4.5-mm-wide implant would result in better implant stability and survival as opposed to the 3.75-mm-wide implant. Because soft tissue around the abutment is left intact with the tissue preservation technique, it was also hypothesized that this procedure would lead to better skin sensibility and less adverse skin reactions. Interestingly, for both the 4.5- and 3.75-mm-wide implant, and both the LIT-TP and the LIT-TR, **chapter 2** reported good, and comparable, 5-year clinical outcomes with few complications and implant survival rates ranging between 95% and 100%. Between subgroups, only minor differences were observed. While implant stability as measured with the implant stability quotient (ISQ), was significantly better for the 4.5-mm-wide implant, implant survival was comparable between the 4.5- and 3.75-mm-wide implant. A similar observation was made by *Kruyt et al.,* evaluating the 3-year outcomes of this patient population. (1) There are several hypotheses which might elucidate the discrepancy between implant stability as measured by ISQ and implant survival. First of all, because of generally high implant survival rates, sample size might have been too small to find a difference between groups. Second, despite (slightly) worse implant stability, implant fixation was still adequate and, therefore, implant loss did not occur. And third, the ISQ measurements did not correlate directly with clinical implant stability. Since ISQ values are affected by several other factors besides implant stability, the relationship between ISQ values and implant stability has been questioned regularly.

(2,3) In a review on ISQ measurements in BAHI patients, Nelissen et al. stated that only trends in ISQ values over time should be interpreted. (2) We should therefore ask ourselves, when comparing ISQ values between patients with different implant designs: does a difference in ISQ reflect a difference in implant stability and would it result in a difference in implant failure? We need to increase our understanding of ISQ measurements and clarify its correlation with implant stability, before continuing to use it as a comparative outcome measure. Furthermore, it would be interesting to investigate the usability of other implant stability measurement systems such as the advance system for implant stability testing (ASIST) and the Periotest. (4,5)

Based on the findings in **chapter 2**, neither the 4.5-mm-wide implant, nor the LIT-TP did improve clinical outcomes when compared to their predecessors. However, as mentioned before, sample size was probably too small to detect a difference in implant survival between implant designs. Only one other comparative study on implant survival in 4.5- and 3.75-mm-wide implants has been performed. This study reported comparable survival rates between implant designs. (6) To establish whether 4.5-mm-wide implants are truly superior to 3.75-mm-wide implants in terms of implant survival, a comparative study with a large study population should be conducted. Unfortunately, it is not feasible to conduct such a study, with relatively few BAHI implantations performed each year and the production of the 3.75-mm-wide implants being discontinued. Therefore, in the Radboud university medical center, an alternative study on implant survival was designed: a retrospective study evaluating implant survival of all 3.75-mm-wide implants placed using a LIT-TP. At the time of writing, results were not yet available. It would however be interesting to compare the results of this study, to the findings of Dun et al., who evaluated implant survival in over a thousand 3.75-mm-wide implants. (7) As for the LIT-TP and the LIT-TR, no differences in skin sensibility and adverse skin reactions were observed between groups at the current 5-year evaluation. However, previous literature showed added clinical value of the LIT-TP in terms of shorter surgery time, faster wound healing and less numbness when compared with the LIT-TR. (8-10). The LIT-TP is therefore considered the gold standard surgical technique for implanting BAHI's.

In addition to an evaluation of the state of the art in terms of clinical outcomes, **chapter 3** investigated HRQoL in 75 patients who underwent implantation with a 4.5-mm-wide implant using either the LIT-TP or the LIT-TR. HRQoL is not only considered an important measure for efficacy but is also of crucial importance for reimbursement reasons. With annually rising health care costs, health insurers increasingly demand cost-effectiveness analyses upon deciding on resource allocation. (11-14) **Chapter 3** evaluated HRQoL with the Glasgow Benefit Inventory (GBI), Glasgow Health Status Inventory (GHSI), and sound processor use. The questionnaires and sound processor use were determined at different time points, and among and across different indication groups. After BAHI implantation, increased scores on the GBI and GHSI were observed in every indication group, suggesting improved HRQoL after BAHI implantation in patients with bilateral conductive/mixed hearing loss, patients with unilateral conductive/mixed hearing loss and patients with single-

sided deafness. GBI and GHSI scores were consistent over time, with a total follow-up of 12 and 36 months, respectively. At 36 months, sound processor usage rates were high for every indication group with a median sound processor use of 15 hours/day (IQR 10) for the total study population. Only in the patients with single-sided deafness, sound processor use decreased over time. The latter finding is useful to keep in mind when counseling patients with single-sided deafness applying for a BAHI. The findings in **chapter 3** thus demonstrated that in selected patients, the BAHI system results in an improved HRQoL, which is stable over time and independent of indication. Because of the consistency in GBI and GHSI outcomes over time, questionnaire outcomes can be compared across studies, independent of the time point of assessment. This simplifies performing a meta-analysis and comparing HRQoL outcomes between BAHI implantation and other types of hearing rehabilitation such as surgical reconstruction and conventional hearing aids. For future studies, it would also be interesting to compare HRQoL data between percutaneous and transcutaneous BAHI and include this in a cost-benefit analysis.

Taking the outcomes of **chapters 2 and 3** together, the current percutaneous BAHI system and surgical procedure result in good clinical outcomes with few and minor postoperative complications, as well as improved and stable hearing-related quality of life and high sound processor usage rates.

Part II: Evaluation of a minimally invasive surgical technique

In view of the favorable outcomes described above, the question has been raised whether there is any value for new developments in implant designs and surgical techniques within the BAHI field. Yet, a new, even less invasive surgical technique, was already developed. minimally invasive Ponto surgery or MIPS was hypothesized to decrease surgery time and adverse skin reactions, and retain skin sensibility better than with the LIT-TP. However, before implementing a new technique into clinical practice, it is of importance to investigate the following: as a first, does the new technique has added value over the current gold standard? And, second, in case of added value, do the benefits of the new technique outweigh the (if applicable) additional costs?

Chapter 4 evaluated the clinical value of MIPS compared with the LIT-TP. MIPS was found to result in a shorter surgery time, better cosmetic outcomes, comparable skin sensibility and adverse skin reactions, but also in a higher implant loss rate of 12%. The study was not powered for implant survival and the difference in implant loss rate did not reach statistical significance. However, the implant loss rate raised our concern, especially since other studies reported high implant loss rates up to 35% after MIPS. (15-17) It was hypothesized that the higher implant loss rate would be a result of 1) the presence of interposed periosteum, 2) incorrect angulation of the drill and/or implant, or 3) inadequate bone cooling resulting in thermal injury to bone tissue and necrosis and

thus impaired osseointegration. Since implant survival is one of the most important outcomes of BAHI surgery, the problem of impaired implant survival needed to be solved first before pursuing any further clinical studies on MIPS. The manufacturer modified the design and shape of the drill bits in order to improve drill efficiency and osteotomy preparation. Furthermore, in an attempt to decrease heat generation, a 3-step drilling protocol was utilized instead of the previously advocated 2-step drilling. In **chapter 5**, outcomes of this modified drill set (m-MIPS) and the 3-step drilling protocol were evaluated and compared to the LIT-TP and original MIPS (o-MIPS). **Chapter 5** found comparable implant survival rates between m-MIPS and the LIT-TP. Although this finding seems promising, caution should be taken when interpreting this result because the study was underpowered with respect to implant survival. With m-MIPS, surgery time was reduced from 21 to 6 minutes, but all other clinical outcomes such as intra-operative complications, adverse skin reactions and skin sensibility were comparable with the LIT-TP. These findings are in line with results of studies comparing o-MIPS with the LIT-TP. (17,18) The only benefit of MIPS, as observed in literature, is reduced surgery time. Since the LIT-TP is already a short procedure, the clinical value of reduced surgery time is limited. On top of this, the LIT-TP is known for its good implant survival rate, while the true survival rate of m-MIPS is still unsure. Therefore, based on current research, m-MIPS seems to be a safe procedure to implant BAHI's but does not show added clinical value over the LIT-TP, the current gold standard surgical technique in both children and adults. Furthermore, it is debatable whether m-MIPS would be an appropriate technique in every patient and in every setting. In young children for instance, two fixtures are placed instead of one, so that the spare fixture can be used in case of future implant loss. In these children, advocating the LIT-TP seems more sensible than performing two separate punches. M-MIPS is also less suitable in cases where intraoperative visibility is important, such as in patients with thin temporal bone, cranial malformations or in patients with CHARGE syndrome which is associated with venous anomalies of the temporal bone. (19) Finally, surgeons need to be able to convert m-MIPS to the LIT-TP in case of intra-operative complications. Therefore, it is of importance to train surgical residents in performing the LIT-TP. Because of the abovementioned issues, m-MIPS has not (yet) been adopted as a surgical technique to insert BAHIs in the Radboud university medical center. For future developments, it is of importance to determine the added value and cost-effectiveness first, before implementing a new implant or surgical technique into clinical practice. Because of the excellent clinical outcomes of the 4.5-m-wide implant and the LIT-TP, it will be rather challenging to create new implant designs and surgical techniques which add significant value to clinical practice at a reasonable price. However, we should bear in mind that most research, including the chapters in the current thesis, is performed on an healthy adult patient population. (20) For certain patient groups, such as children and patients with developmental delay, higher implant loss rates and worse soft tissue tolerability, have been reported. (7) For these selected patient groups, there is certainly room for further improvement of clinical outcomes. Based on the cost-effectiveness study of Kruyt et al., enhancement of implant survival will probably lead to more cost reduction than the improvement of soft tissue tolerability. (21) The challenge of improving implant survival however, is

that large patient populations are needed to prove that a new implant or technique truly enhances survival. This especially complicates research when investigating selected, and thus small, patient groups.

Part III: Optimizing care

As stated above, in certain patient groups using the BAHI system, there is still room to improve outcomes. In an attempt to introduce individualized care, part III of this thesis focused on enhancing outcomes in two of these groups and explored patient preferences in relation to sound processor loading time.

In **chapter 6**, a clinical evaluation of 14 patients treated for idiopathic pain around the abutment, was performed. Idiopathic pain is a rare but burdensome symptom which often leads to implant loss or elective removal of the implant. Based on this evaluation, a treatment schedule with oral antibiotic combination therapy was proposed. Since the choice for this treatment was based on a retrospective review of only 14 patients, it is questionable whether this treatment schedule will be truly effective. It would therefore be interesting to collect clinical data on more patients with idiopathic pain, also from other institutions. In case of persistent pain despite oral antibiotic combination therapy, referral to a specialized pain management team can be considered prior to removal of the implant. Further research into the etiology behind idiopathic pain could be helpful in finding an adequate treatment for this symptom. Since inflammation of the deeper soft tissue layers spreading towards the bony tissue, is one of the proposed etiologies, we could, for example, perform microbiological analyses on the soft-tissue layers around the abutment in patients with idiopathic pain. In line with the study of Calon et al., who tried to identify a microbiological profile associated with adverse skin reactions, we might be able to describe a profile associated with idiopathic pain. (22) Based on such a microbiota profile of the surrounding skin and peri-abutment space, an adequate antibiotic regimen can be determined.

Chapter 7 provides an overview of sound localization performance in 15 bilateral BAHI users. The effectiveness of a second BCD in case of bilateral conductive/mixed hearing loss has been questioned for decades since a BCD will stimulate both cochleas almost equally due to the small intracranial attenuation. For the same reason, it has been thought that patients with bilateral BCDs are less capable of localizing sounds. However, previous research already showed that bilateral BCDs improve speech understanding in noise, hearing-related quality of life and sound localization. In these studies patients were able to lateralize sounds, e.g. determining whether a sound was coming from the left or right side but not more precise than that. **Chapter 7** demonstrated that some patients with bilateral BCDs are capable of localizing sounds, almost as accurate as normal hearing listeners. In this study, all patients with quite accurate localization behavior were bilaterally

rehabilitated by the age of 8. This suggests that, when bilateral hearing rehabilitation is realized during early/mid childhood, patients with a bilateral conductive or mixed hearing loss might be able to develop (fairly) accurate sound localization skills. Enhancing sound localization skills and speech recognition-in-noise relatively early in life might be advantageous for speech- and language development and for so-called unintentional learning. Potentially, this improved auditory input from the child's environment might have a positive effect on non-verbal IQ, an effect which has been observed in children provided with bilateral cochlear implants instead of just one. (23) Unfortunately, due to the limited data, it is still unclear whether bilateral implantation should indeed be performed before a certain age to assure adequate localization skills. On the other hand, the improved speech understanding in noise, hearing-related quality of life, and sound localization performance, should be reason enough to provide bilateral hearing rehabilitation (two BCDs on a softband) to children with bilateral congenital conductive hearing loss, as soon as possible after diagnosis.

Following the trend in BAHI care towards earlier sound processor loading after BAHI implantation, **chapter 8** assessed the preferred loading time in 60 patients undergoing percutaneous BAHI surgery. The rationale behind shorter loading times is that it allows for earlier hearing rehabilitation and enhances efficiency when combined with the one-week postoperative visit or performed on the same day as surgery. It is thought that this will reduce hospital costs and will increase patient satisfaction.(24,25) However, according to **chapter 8**, there is quite some variation in preferred loading time among patients. Depending on the time-point of assessment, loading within the first week postoperatively was preferred by 40% to 50% of patients, while loading around three weeks after surgery was preferred by 35% to 47.5% of patients. The most important lesson learnt from this investigation is that patient preferences vary and cannot (always) be predicted beforehand. It is of course not always possible to adapt all clinical procedures to every individual patient, but when we are aware of our patients' preferences, individualized care is feasible for most patients. This article emphasizes the importance of evaluating patient preferences before implementing new treatment protocols or techniques.

Concluding remarks and considerations for the future

The currently used percutaneous BAHI system, implanted using the LIT-TP, in combination with loading after 3 weeks shows excellent clinical outcomes and improves hearing-related quality of life in indicated *adult* patients. Following these excellent results, new implant designs and surgical techniques will probably have limited impact on clinical outcomes in adults. This also seems applicable for m-MIPS which, although it implies less surgical time needed, did not show added clinical value when compared with the LIT-TP and was therefore not (yet) implemented in clinical practice in the Radboud university medical center.

Over the last few years, manufacturers of BAHI-systems are focusing on the development of new, active, transcutaneous systems. (26,27) For researchers, the task awaits to evaluate the safety and added value of these devices when compared to percutaneous BAHI-systems, in terms of clinical, audiological and (hearing-related) quality of life outcomes. Furthermore, the cost of ownership needs to be assessed and compared. Because of its good clinical outcomes, simple surgical procedure and MRI-compatibility, the percutaneous BAHI will probably remain a widely used hearing rehabilitation system. However, certain patient groups at risk for developing complications, might benefit from a transcutaneous option, as the intact skin prevents implant loss and adverse skin reactions. In addition, future research should focus more on efficiency of care and the implementation of patient-centered care, since there is considerable room for improvement in these areas. For instance, BAHI implantation in children below the age of ten is currently performed in two stages. It would be interesting to investigate the safety of one-stage surgery in this age-group, since it reduces anesthetic exposure and financial costs, and allows for earlier hearing rehabilitation. Furthermore, with surgery times of around twenty minutes and procedures mainly being performed under local anesthesia, it would be interesting to investigate whether BAHI insertion may also be conducted in an outpatient clinic setting instead of the operating theater. Office-based BAHI surgery probably results in lower facility costs and is less time-consuming for both surgeon and patient when compared to BAHI procedures performed in the operating theater. (28) We should however carefully determine whether office-based BAHI procedures are as safe as operating room procedures, especially in terms of sterility, surgical site infections and handling perioperative complications. Furthermore, all personnel preparing or assisting the office-based BAHI procedure should be qualified and properly trained in order to guarantee safety and good quality of care. Next to exploring the possibility of office-based procedures, efficiency might be further improved by changing sound processor loading protocols. Over the past decades, sound processor loading times have decreased and recent literature even reports next-day loading as a safe and feasible option. (24,25,29) These findings need to be confirmed in larger studies, but if next-day loading is feasible, then same-day loading might be as well. Same-day loading results in fewer visits and allows for earlier hearing rehabilitation, which is especially interesting for patients with a large travel distance towards the hospital. Another way to reduce hospital visits is by introducing remote care. An example of remote care could be a mobile application through which patients can send information regarding their BAHI, e.g. implant-related complaints or photos of the abutment-surrounding skin, to a medical professional. Answering questions and/or prescribing treatment through such an application, could reduce the number of hospital visits and related costs. However, when introducing new developments such as remote care, we should be aware of the preferences of the individual patient. Not every patient appreciates communication through an application, and some patients prefer a hospital visit over remote care. It is therefore important to incorporate personalized care into our clinical practice and to be aware of our patients' preferences prior to implementing new procedures.

In summary, the currently used 4.5-mm-wide implant and the LIT-TP for implanting BAHI's result in excellent clinical outcomes and good hearing-related quality of life outcomes in the healthy adult patient population. Outcomes of specific patient groups, such as children and patients with developmental delay can however still be improved. In addition, future research should focus on individualized care and enhancing efficiency of care.

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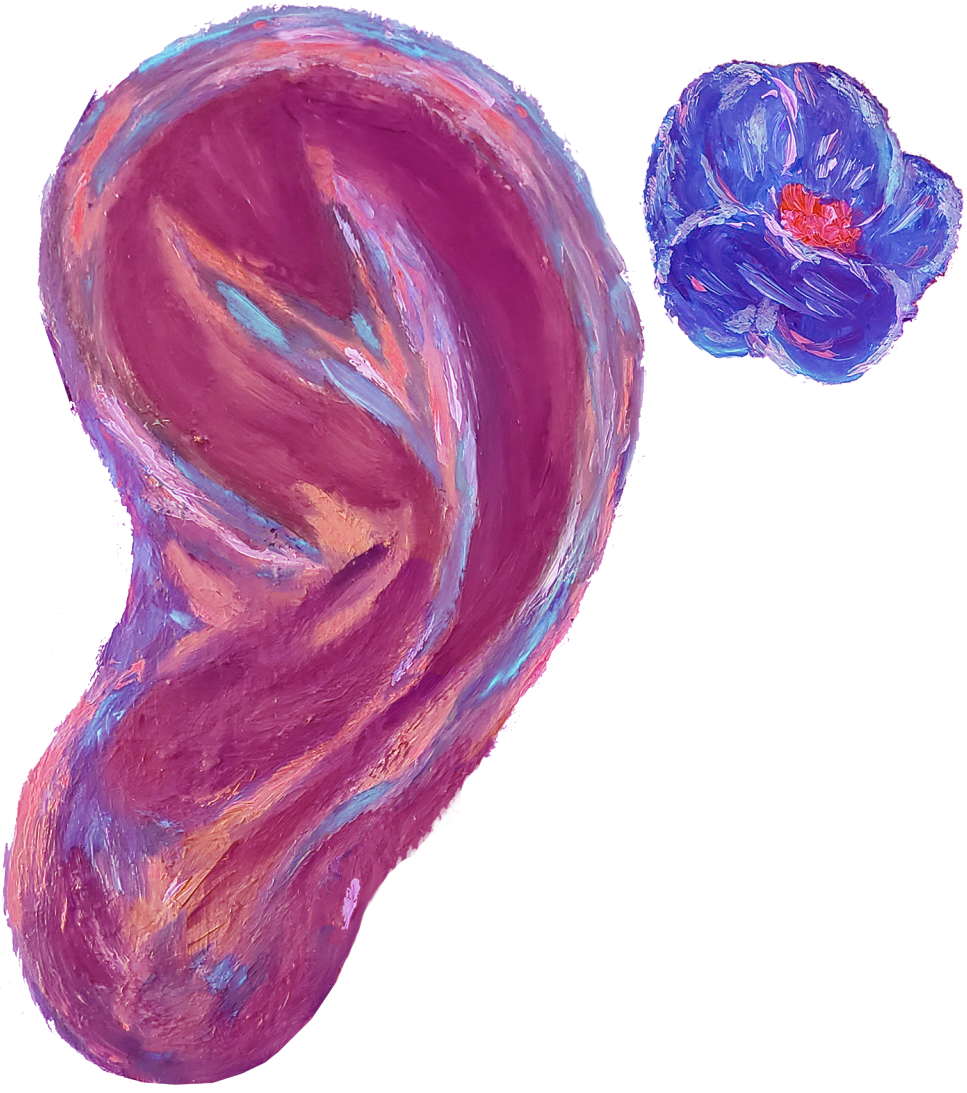


CHAPTER 10

Summary

Since its first implantation in 1977, the percutaneous bone-anchored hearing implant (BAHI) has evolved into a safe and efficient hearing rehabilitation system for indicated patients. Nowadays, implantation with a 4.5-mm-wide implant using the linear incision technique with soft tissue preservation (LIT-TP) is considered the gold standard procedure. Although previous research has demonstrated favorable postoperative outcomes of this wide diameter implant and the LIT-TP, data on long-term clinical outcomes and hearing-related quality of life (HRQoL) are scarce. Furthermore, despite the favorable outcomes of the current BAHI system, there is still room for improvement with regard to both postoperative complications such as adverse skin reactions and idiopathic pain, as well as audiological outcomes and patient centered care. The first part of this thesis (**chapter 2 and 3**) aimed to fill the knowledge gap concerning long-term clinical and HRQoL outcomes of the currently used BAHI system. The second part (**chapter 4 and 5**) evaluated clinical outcomes of minimally invasive Ponto surgery (MIPS), a new minimally invasive surgical technique which was developed in order to further decrease postoperative complications. The third and last part of this thesis (**chapter 6, 7 and 8**) focused on exploring current clinical challenges and patient preferences.

Chapter 2 compared the 5-year clinical outcomes of a currently used 4.5-mm-wide implant (Wide Ponto® implant, Oticon Medical AB) and the LIT-TP, with the previous generation 3.75-mm-wide implant (Ponto® implant, Oticon Medical AB) and the linear incision technique with soft tissue reduction (LIT-TR), respectively. A total of 68 patients participated in a prospective single follow-up visit 5 years after BAHI implantation. The study demonstrated good and comparable clinical outcomes for both implant types and both surgical techniques, with excellent implant survival rates ranging between 95% and 100%, and only few postoperative complications. No significant differences in adverse skin reactions nor skin sensibility were observed between groups. In both implant types, implant stability as measured with the implant stability quotient (ISQ) increased over time. Although ISQ values were slightly better for the 4.5-mm-wide implant when compared with the 3.75-mm-wide implant, implant survival was comparable between implant types. Possibly, sample size was too small to detect a difference in implant survival between implant designs. The findings of this study indicated that both the 3.75- and 4.5-mm-wide implant, as well as the LIT-TR and the LIT-TP procedures are safe on the long term and result in good implant survival rates and postoperative outcomes. Based on previous literature demonstrating added clinical value of the LIT-TP over the LIT-TR in terms of shorter surgery time, faster wound healing and better skin sensibility, LIT-TP is currently preferred over LIT-TR.

Chapter 3 evaluated prospectively collected data on HRQoL and sound processor use in 75 patients who were implanted with a percutaneous BAHI (previous generation 3.75-mm Ponto® implant or the newer 4.5-mm Wide Ponto® implant, Oticon Medical AB) using either the LIT-TP or LIT-TR. Sound processor use and HRQoL, evaluated by means of the Glasgow Health Status Inventory (GHSI) and Glasgow Benefit Inventory (GBI), were assessed at different time points and among and

across different indication groups. The GBI was assessed at 3 and 12 months postoperatively, the GHSI preoperatively and at 6 and 36 months postoperatively and sound processor use at 6, 12 and 36 months. For the total study population, as well as for every indication group, increased scores on the GBI and the GHSI were observed after BAHI implantation. This suggested that HRQoL improved after BAHI implantation in patients with bilateral conductive/mixed hearing loss, patients with unilateral conductive/mixed hearing loss and patients with single-sided deafness. Over time, GBI and GHSI scores were consistent, with a total follow-up of 12 and 36 months, respectively. At 36 months, median sound processor use was 15 hours/day (IQR 10) for the total study population and only one non-user was reported. Between 6 and 36 months, sound processor use was stable over time, except for patients with single-sided deafness in which sound processor use decreased. Patients with bilateral hearing loss used their sound processors more frequently and showed greater improvement on the GHSI total score than patients with unilateral hearing loss. This study thus demonstrated that BAHI implantation results in improved HRQoL, at least up to three years after implantation, in patients with both unilateral and bilateral conductive/mixed hearing loss, and in patients with single-sided deafness. HRQoL is stable over time and despite differences between indication groups, sound processor usage rates are high for every indication.

Chapter 4 evaluated the 6-month clinical outcomes of MIPS and compared them with the outcomes of the LIT-TP, the current gold standard surgical technique. On beforehand, MIPS was thought to result in shorter surgery time, less adverse skin reactions and better skin sensibility when compared with the LIT-TP. A prospective comparative study was designed in order to investigate this hypothesis. A total of 25 adult patients were prospectively included and underwent BAHI implantation using MIPS with a 2-step drilling protocol. The control group consisted of 25 patients who previously participated in another clinical trial and already underwent implantation using the LIT-TP. In both groups, a Wide Ponto implant® (diameter 4.5mm, Oticon Medical AB) was implanted and follow-up schemes were similar. In this study, MIPS resulted in a shorter surgery time, better cosmetic outcomes, comparable skin sensibility and adverse skin reactions, but also in a statistically non-significant, higher implant loss rate of 12%. This higher implant loss rate raised concern, especially because other studies also reported high implant loss rates after MIPS. With implant survival being one of the most important outcomes of BAHI surgery, the problem of decreased implant survival needed to be solved prior to advocating further clinical studies on MIPS. In order to improve drill efficiency and osteotomy preparation, the design and shape of the drill bits were modified by the manufacturer. In addition, a 3-step drilling protocol was performed instead of the previously used 2-step drilling, aiming to decrease excessive heat generation.

Chapter 5 investigated the outcomes of the modified MIPS drill set (m-MIPS) and the 3-step drilling protocol and compared these with the outcomes of the LIT-TP and the original MIPS drill set (o-MIPS) with 2-step drilling protocol. In this study, implant survival rates were comparable between m-MIPS and the LIT-TP. This outcome should however be interpreted with care since this

study was not statistically powered for implant survival. M-MIPS reduced surgery time with 70% (21 to 6 minutes) when compared with the LIT-TP. The clinical value of this reduction in surgery time seems limited, since the LIT-TP is already a short procedure. All other clinical outcomes (intra-operative complications, adverse skin reactions and skin sensibility) were however comparable between m-MIPS and the LIT-TP. Based on these findings, m-MIPS seemed to be a safe procedure to implant BAHI's, but at this moment, the added value of m-MIPS over the LIT-TP is limited, since only surgery time is reduced and all other clinical outcomes are comparable. Furthermore, while the LIT-TP is known for its good implant survival, the survival rate of m-MIPS has not yet been thoroughly investigated. Therefore, m-MIPS has not (yet) been adopted as a surgical technique to insert BAHIs at the Radboud university medical center.

Chapter 6 presented a retrospective chart analysis evaluating the data of 14 patients treated for idiopathic pain around the abutment, a rare but burdensome symptom often resulting in spontaneous implant loss or surgical removal. In literature, no adequate treatment strategy has been described to alleviate this pain. All included patients received treatment with oral antibiotics. Eleven patients were initially treated with antibiotic combination therapy consisting of Ciprofloxacin 500mg twice daily for two weeks and Clindamycin 300mg three times a day for four weeks. In one of these patients, the antibiotic combination therapy was shortened due to an allergic reaction and in another patient abutment change was performed together with the initiation of antibiotic treatment After antibiotic combination therapy, pain resolved in six out of eleven patients. The remaining three patients received either antibiotic monotherapy or a modified antibiotic combination therapy scheme, all with limited effects. In case of persistent pain (8 patients) after initial treatment, other pain management therapies were attempted, however all with only limited effect. A prolongation of the antibiotic combination therapy did not resolve the pain. Because of persistent pain, six patients underwent elective removal of the implant. In two patients spontaneous implant loss occurred. In two of the four patients who underwent reimplantation, pain relapsed. The clinical implications of the findings in this study are uncertain, given the small number of patients and retrospective nature. Furthermore, resolved pain after systemic antibiotic treatment might be a result of a placebo-effect or because the pain was induced by a self-limiting disease. However, given the relevance of hearing rehabilitation with BAHI for these patients, weighed against the non-invasiveness of the prolonged medical treatment, we suggest to prescribe oral antibiotic combination treatment prior to implant removal. However, if pain persists, an additional treatment with antibiotics doesn't seem sensible and is therefore not recommended. In case of persistent pain despite systemic antibiotic treatment, referral to a specialized pain team might be an option before deciding to surgically remove the implant. Especially since pain might relapse following reimplantation.

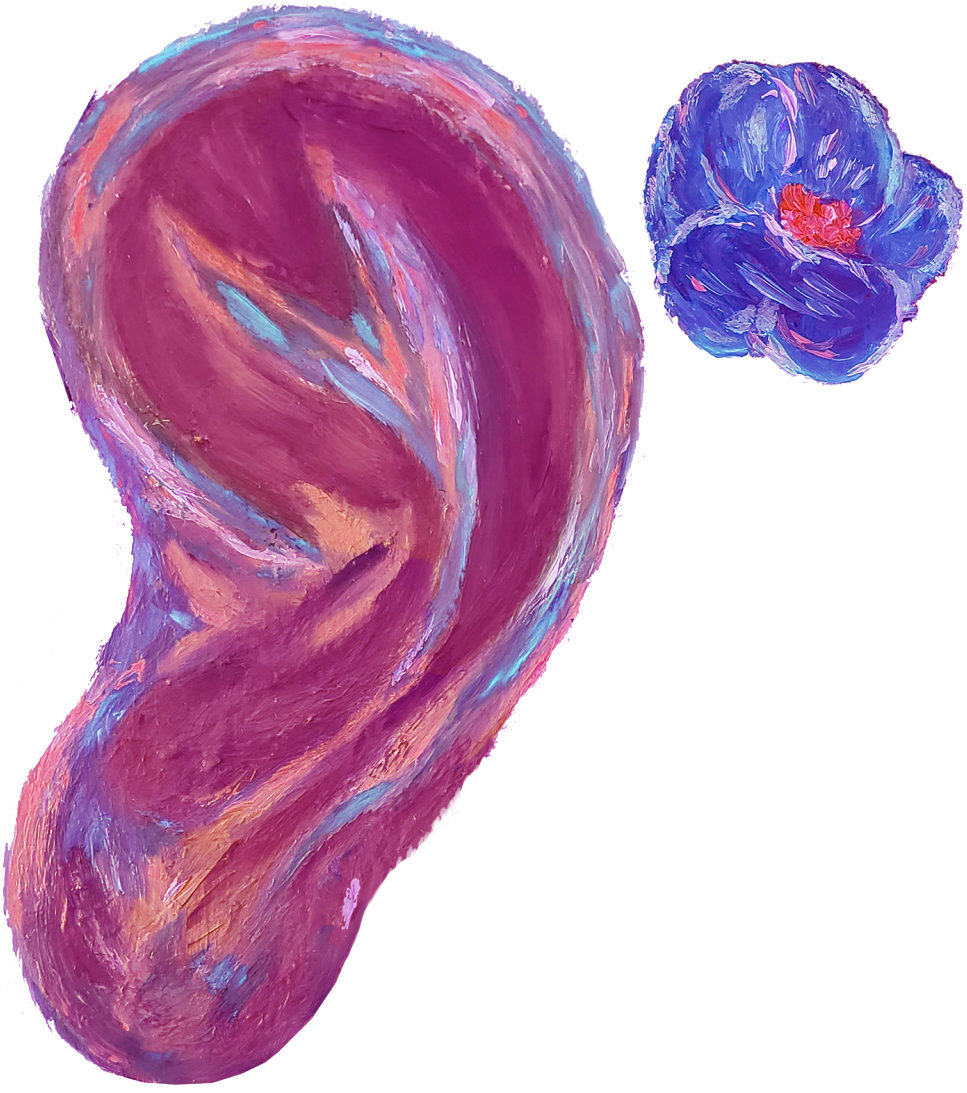
For decades, it has been thought that patients with bilateral BAHIs are less capable of localizing sounds, since one BAHI will stimulate both cochleas almost equally due to small intracranial

attenuation. **Chapter 7** investigated this hypothesis by determining sound localization ability in patients bilaterally fitted with BAHIs. Additionally, this study explored methods to improve localization accuracy. Fifteen adult patients with bilateral congenital or acquired conductive/mixed hearing loss were included. First, sound localization ability was assessed at baseline. Hereafter, a second listening program was added to both sound processors with settings to optimize localizing sounds. At one month, sound localization was assessed again and localization was practiced with a series of sounds with visual feedback followed by a sound localization evaluation at three months follow-up. Interestingly, these tests demonstrated that some patients with bilateral BAHIs were capable of localizing sounds, almost as accurate as normal hearing listeners. One third of the patients was able to localize sounds (quite) accurately, while the majority of these experienced bilateral BAHI users was able to lateralize sounds (i.e. identify whether sounds were coming from the left or right side). All study patients with quite accurate localization behavior were bilaterally rehabilitated by the age of 8. This suggests that, when bilateral hearing rehabilitation is realized during early/mid childhood, patients with a bilateral conductive or mixed hearing loss might be able to develop (fairly) accurate sound localization skills. Unfortunately, in patients less capable of localizing sounds, optimizing sound processor settings and the short practice session did not improve localization performance.

Following the trend in BAHI care towards earlier sound processor loading after implantation, **chapter 8** assessed the preferred loading time in 60 patients undergoing percutaneous BAHI surgery. Currently, sound processor loading is performed around three weeks after surgery. The rationale behind shorter loading times is that it allows for earlier hearing rehabilitation and enhances efficiency when combined with the one-week postoperative visit or performed on the same day as surgery. It is thought that this will reduce hospital costs and will increase patient satisfaction. This prospective questionnaire study assessed the preoperative and postoperative preferred loading time and the postoperative change in these 60 patients. This study showed that there was quite some variation in preferred loading time among patients. Depending on the time-point of assessment, loading within the first week postoperatively was preferred by 40% to 50% of patients, while loading around three weeks after surgery was preferred by 35% to 47.5% of patients. Furthermore, the number of patients preferring earlier loading than currently advocated, declined early loading postoperatively. Thus, approximately half of all patients preferred sound processor loading within one week after BAHI surgery. To cater both to our patients' preferences and to improve hospital efficiency, sound processor loading one week (instead of three weeks) after surgery might be implemented. However, it is important to realize that preferences differed among patients. This study emphasized the importance of evaluating patient preferences before implementing new treatment protocols or techniques.

The current thesis evaluated clinical and hearing-related quality of life outcomes following BAHI surgery according to the current golden standard, investigated a new minimally invasive surgical

technique and explored remaining clinical challenges. Following the excellent results of the currently used implants and surgical procedure, new implant designs and surgical techniques will probably have limited impact on clinical outcomes in adults. Therefore, the safety and added value of newly developed implants and surgical techniques need to be investigated thoroughly and critically apraised. Additionally, future research should focus more on improving outcomes in specific patient groups, efficiency of care and the implementation of patient-centered care, since there is considerable room for improvement in these areas.



CHAPTER 11

Samenvatting

Het percutane botverankerde hoorimplantaat (BAHI) werd voor het eerst geïmplanteerd in 1977 en staat tegenwoordig bekend als een veilige en efficiënte methode om het gehoor te revalideren. De gouden standaard operatie procedure bestaat uit het implanteren van een 4,5mm breed implantaat volgens de lineaire incisie techniek met behoud van weefsel (weefselsparende techniek). Uit eerdere wetenschappelijk onderzoeken is bekend dat deze procedure leidt tot goede klinische uitkomsten op de korte termijn. Over gehoor-gerelateerde kwaliteit van leven en over klinische uitkomsten op de lange termijn is nog weinig bekend. Daarnaast is er, ondanks de goede uitkomsten op korte termijn, nog steeds verbetering mogelijk op het gebied van postoperatieve complicaties zoals klinische relevante huidreacties en idiopathische pijn, audiologische uitkomsten en patiëntgerichte zorg. Het eerste deel van dit proefschrift (**hoofdstuk 2 en 3**) had als doel het kennis tekort omtrent lange termijn resultaten en gehoor gerelateerde kwaliteit van leven te onderzoeken. In het tweede deel (**hoofdstuk 4 en 5**) werden de klinische uitkomsten van een nieuwe minimaal invasieve chirurgische techniek (Minimally Invasive Ponto Surgery (MIPS)) onderzocht. Het derde deel van dit proefschrift (**hoofdstuk 6, 7 en 8**) richtte zich op het exploreren van huidige klinische problemen en het onderzoeken van de voorkeuren van patiënten rondom het aanmeten van de geluidsprocessor.

In **hoofdstuk 2** werden de 5-jaars klinische uitkomsten van het momenteel gebruikte 4,5mm brede implantaat (Wide Ponto® implant, Oticon Medical AB) en de weefselsparende techniek vergeleken met respectievelijk het 3,75mm brede implantaat (Ponto® implant, Oticon Medical AB) en de lineaire incisietechniek met weefselreductie (weefselreductie techniek). Een totaal van 68 patiënten nam deel aan deze prospectieve studie met een eenmalig follow-up bezoek 5 jaar na implantatie. De resultaten demonstreerden goede en vergelijkbare klinische lange termijn uitkomsten voor beide implantaten en beide chirurgische technieken. Implantaatoverleving was 95%-100% en het aantal postoperatieve complicaties was beperkt. Wat betreft klinisch relevante huidreacties of gevoelloosheid van de huid, werden geen significante verschillen gevonden tussen de groepen. Implantaat stabiliteit, zoals gemeten met de implant stabiliteit quotiënt (ISQ), verbeterde gedurende de follow-up. Ondanks hogere ISQ waarden bij het 4,5mm brede implantaat, was de implantaatoverleving gelijk voor het 4,5mm brede en het 3,75mm brede implantaat. Mogelijk was de studie populatie te klein om een verschil in implantaatverlies te ontdekken tussen beide groepen. De resultaten van dit onderzoek impliceren dat beide implantaat typen en beide chirurgische technieken op de lange termijn veilig zijn en leiden tot een goede implantaatoverleving en weinig postoperatieve complicaties. De weefselsparende techniek wordt beschouwd als de gouden standaard procedure, aangezien eerder wetenschappelijk onderzoek heeft aangetoond dat de weefselsparende techniek een snellere procedure is en resulteert in snellere wondgenezing en minder gevoelloosheid van de huid in vergelijking met de weefselreductie techniek.

Hoofdstuk 3 omvat een evaluatie van prospectief verzamelde data omtrent gehoor-gerelateerde kwaliteit van leven en gebruik van de geluidsprocessor in 75 patiënten met een BAHI (3,75mm

Ponto® implantaat of 4,5mm Wide Ponto® implantaat, Oticon Medical AB), geïmplanteerd middels weefselsparende of weefselreductie techniek). Gebruik van de geluidsprocessor en gehoor-gerelateerde kwaliteit van leven werden onderzocht met behulp van de Glasgow Health Status Inventory (GHSI) en de Glasgow Benefit Inventory (GBI) vragenlijsten. De GBI werd 3 en 12 maanden na de operatie afgenomen. De GHSI werd vóórde operatie afgenomen en 6 en 36 maanden na de ingreep. Op 6, 12 en 36 maanden na de operatie werd gevraagd naar het gebruik van de geluidsprocessor. De resultaten werden geanalyseerd voor de totale studie populatie en per indicatie groep. Na BAHI implantatie verbeterden de GHSI en GBI scores voor zowel de gehele studie populatie als voor iedere indicatie groep. Dit impliceert dat de BAHI resulteert in een verbeterde gehoor-gerelateerde kwaliteit van leven in patiënten met een bilateraal conductief/gemengd gehoorverlies, in patiënten met een eenzijdig conductief/gemengd gehoorverlies en in patiënten met een eenzijdige doofheid. GBI en GHSI scores waren consistent over de gehele follow-up periode met een totale follow-up van respectievelijk 12 en 36 maanden. Na 36 maanden follow-up, was het gemiddelde geluidsprocessor gebruik 15 uur per dag (IQR 10) in de totale studie populatie en maar één patiënt gebruikt zijn geluidsprocessor helemaal niet. Afgezien van een afname in het gebruik van de geluidsprocessor in patiënten met eenzijdige doofheid, was het gebruik in de overige indicatie groepen stabiel. Patiënten met bilateraal gehoorverlies gebruikten hun geluidsprocessoren wel vaker dan patiënten met een eenzijdig gehoorverlies.
Gebaseerd op deze resultaten, resulteerde implantatie van een BAHI dus in een verbetering van de gehoor-gerelateerde kwaliteit van leven, in ieder geval tot drie jaar na implantatie, in zowel patiënten met bilateraal conductief/gemengd gehoorverlies, als patiënten met eenzijdig conductief/gemengd gehoorverlies en in patiënten met eenzijdige doofheid. Ondanks kleine verschillen tussen indicatiegroepen, was de gehoor-gerelateerde kwaliteit van leven stabiel en werd de geluidsprocessor in hoge mate gebruikt gedurende drie jaar na de BAHI operatie.

In **hoofdstuk 4** werden de 6-maanden klinische uitkomsten van de MIPS procedure, geëvalueerd en vergeleken met de uitkomsten van de weefselsparende techniek, momenteel beschouwd als de gouden standaard techniek. De hypothese was dat MIPS, in vergelijking met de weefselsparende techniek, een kortere operatieduur zou hebben en zou leiden tot minder klinisch relevante huidreacties en minder gevoelloosheid van de huid. Deze hypothese werd getest met behulp van een prospectief vergelijkende studie. In totaal werden 25 patiënten prospectief geïncludeerd en geïmplanteerd volgens MIPS en een twee-staps boor protocol. De controle groep bestond uit 25 patiënten die in een eerdere prospectieve klinische studie BAHI implantatie volgens de weefselsparende techniek hadden ondergaan. Alle patiënten werden geïmplanteerd met een Wide Ponto implant® (diameter 4,5mm, Oticon Medical AB) en opgevolgd middels een identiek follow-up schema. Op basis van deze studie, was MIPS inderdaad een snellere chirurgische techniek en resulteerde MIPS in betere cosmetische uitkomsten. Er werd geen verschil gevonden wat betreft gevoelloosheid van de huid en het aantal klinisch relevante huidreacties. Er werd echter ook een niet-significant, hoger implantaatverlies (12%) gevonden na MIPS. Dit verhoogde implantaatverlies

baarde zorgen, aangezien ook andere studies een hogere mate van implantaatverlies na implantatie volgens MIPS beschreven. Omdat implantaatverlies één van de belangrijkste uitkomstmaten is van BAHI chirurgie, moest het aantal implantaatverliezen na MIPS eerst omlaag worden gebracht, voordat verder klinisch onderzoek naar deze nieuwe techniek verricht kon worden. Hierop werd de MIPS boor set aangepast door de fabrikant en werd er een drie-staps boor protocol gehanteerd in plaats van een twee-staps boor protocol. Met deze combinatie aan maatregelen werd gepoogd om op een efficiëntere manier te boren en overmatige warmteontwikkeling tijdens het boren tegen te gaan.

In **hoofdstuk 5** werden de uitkomsten van deze aangepaste/gemodificeerde MIPS boor set (m-MIPS) en het drie-staps boor protocol vergeleken met de uitkomsten van zowel de weefselsparende techniek als originele (o-)MIPS en het twee-staps boor protocol. In deze studie werd een vergelijkbare mate van implantaatoverleving gevonden tussen m-MIPS en de weefselsparende techniek. Er is wel voorzichtigheid geboden bij de interpretatie van deze uitkomst, aangezien de statistische 'power' van deze studie onvoldoende was voor het daadwerkelijk aantonen van een verschil in implantaatverlies. In vergelijking met de weefselsparende techniek verkortte m-MIPS de operatieduur met 70% (van 21 naar 6 minuten). De klinische waarde van deze kortere operatieduur is echter beperkt, aangezien de weefselsparende techniek al een korte procedure is. Alle andere klinische uitkomsten (intra-operatieve complicaties, klinisch relevante huidreacties en gevoelloosheid van de huid) waren vergelijkbaar voor m-MIPS en de weefselsparende techniek. Op basis van deze studie lijkt m-MIPS een veilige operatietechniek. Echter heeft de m-MIPS procedure op dit moment slechts beperkte aanvullende waarde ten opzichte van de weefselsparende techniek, aangezien de klinische uitkomsten vrijwel vergelijkbaar zijn. Daarnaast is van de weefselsparende techniek bekend dat deze techniek resulteert in goede implantaatoverleving op korte en lange termijn, terwijl de precieze implantaatoverleving na m-MIPS nog onzeker is. Om deze redenen wordt m-MIPS op dit moment (nog) niet gebruikt in het Radboud universitair medisch centrum is.

Hoofdstuk 6 omvat een retrospectieve studie waarin de data van 14 patiënten, behandeld voor idiopathische pijn rondom het koppelstuk (abutment), werd geëvalueerd. Idiopathische pijn is een zeldzame maar vervelende klacht die regelmatig leidt tot implantaat verlies of electieve explantatie. Helaas is er in de huidige literatuur geen adequate behandeling bekend voor dit vervelende symptoom. Alle geïncludeerde patiënten werden behandeld met antibiotica. Elf van de veertien patiënten werd behandeld met antibiotische combinatie therapie bestaande uit ciprofloxacine 500mg twee maal daags voor twee weken en clindamycine 300mg drie maal daags voor vier weken. Bij één van deze patiënten werd de behandeling ingekort vanwege een allergische reactie op antibiotica en bij een andere patiënt werd gelijktijdig met het starten van de antibiotische behandeling het koppelstuk verwijderd. Na de antibiotische combinatie behandeling verdween de pijn in zes van de elf patiënten. De overige drie patiënten werden behandeld met monotherapie of een aangepaste combinatie therapie, zonder effect op de pijnklachten. In het geval van

persisterende pijn ondanks antibiotica (8 patiënten), werden verschillende andere behandelingen uitgevoerd, zonder resultaat. Ook een verlenging van de antibiotische combinatiekuur hielp niet. In zes patiënten werd het implantaat verwijderd vanwege persisterende pijn en in twee patiënten trad spontaan implantaat verlies op. Twee van de vier patiënten waarbij een herimplantatie plaats vond, kregen opnieuw pijnklachten. Gezien de beperkte studie populatie en de retrospectieve aard van deze studie, waren de klinische implicaties van deze studie moeilijk te duiden. Het verdwijnen van de pijn na antibiotische behandeling kan ook verklaard worden doordat er sprake was van een 'self-limiting disease' of het zogenaamde placebo-effect. Aan de andere kant hebben de meeste BAHI patiënten weinig tot geen andere mogelijkheden tot gehoorrevalidatie en hebben orale antibiotica over het algemeen weinig bijwerkingen. In het geval van idiopathische pijn is daarom een orale antibiotische combinatie therapie te overwegen, vóórdat wordt overgegaan tot het electief verwijderen van het implantaat. Bij persisterende pijn ondanks een antibiotische combinatie behandeling, lijkt voortzetten van de behandeling niet zinvol. Vóórdat er dan wordt besloten om het implantaat chirurgisch te verwijderen, kan een patiënt nog naar een specialistisch pijnteam worden verwezen. Zeker omdat pijn mogelijk terug kan keren na een herimplantatie.

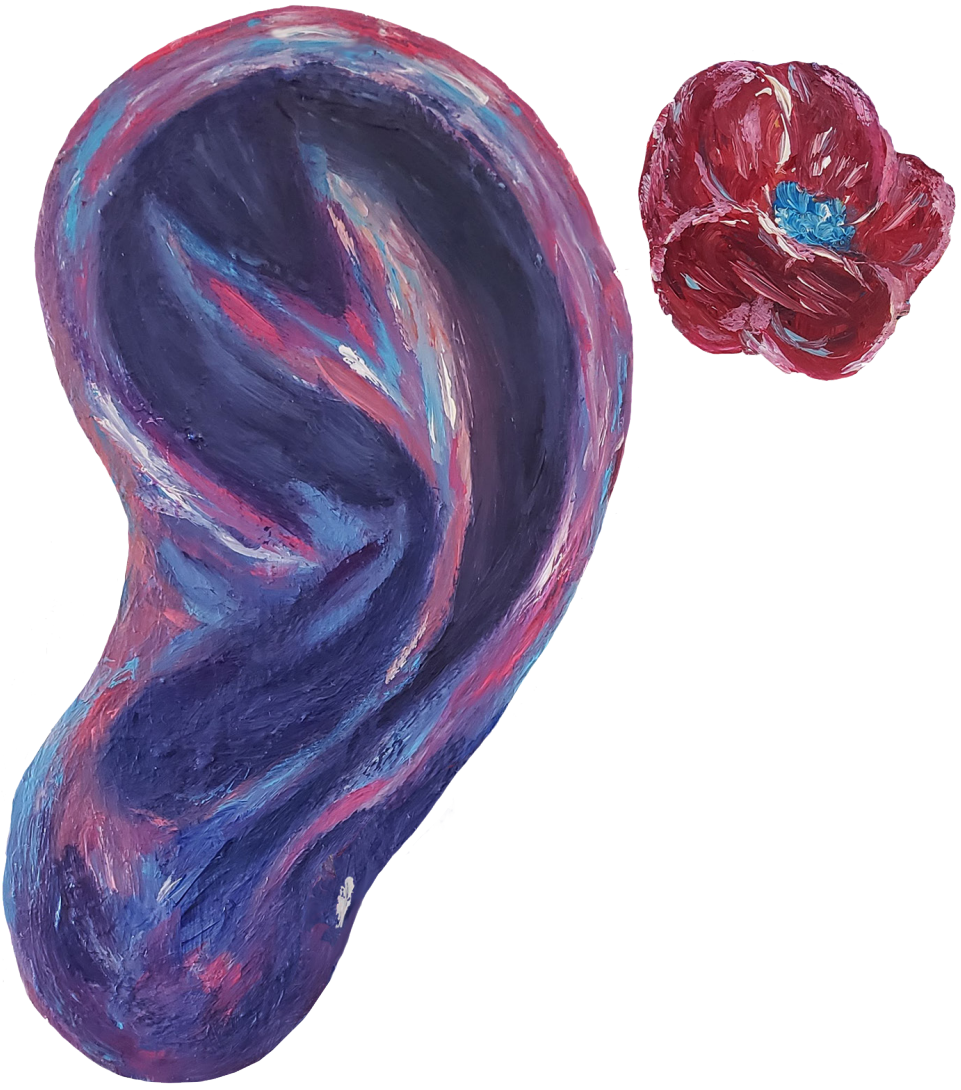
Jarenlang werd gedacht dat patiënten met bilaterale BAHIs geluiden niet goed kunnen lokaliseren omdat één BAHI beide binnenoren al bijna gelijk stimuleert door de beperkte intracraniële verzwakking van geluidstrillingen. In **hoofdstuk 7** werd deze hypothese getoetst met een meting van het geluidslokalisatievermogen in ervaren bilaterale BAHI gebruikers. Aanvullend werden methoden voor het verbeteren van de geluidslokalisatie onderzocht. Vijftien volwassen patiënten met bilateraal congenitaal of verworven conductief/gemengd gehoorverlies werden geïncludeerd. De geluidslokalisatie werd onderzocht tijdens een eerste bezoek, waarna er een tweede luister programma werd toegevoegd aan de geluidsprocessoren om lokalisatievermogen te optimaliseren. Een maand hierna werd het geluidslokalisatievermogen opnieuw getest en werd een korte lokalisatietraining gegeven met behulp van visuele feedback. Drie maanden na de baseline meting werd het geluidslokalisatievermogen nogmaals getest. De baseline lokalisatietest liet zien dat sommige patiënten met bilaterale BAHIs geluiden bijna net zo goed konden lokaliseren als normaalhorenden. Een derde van de patiënten kon geluiden redelijk accuraat lokaliseren en de meerderheid van de patiënten kon geluiden lateraliseren (dat wil zeggen aangeven of een geluid van links of rechts kwam, maar niet nauwkeuriger dan dat). Alle patiënten die geluid redelijk goed konden lokaliseren waren vóór hun achtste levensjaar bilateraal gerevalideerd. Dit impliceert mogelijk dat kinderen met een bilateraal conductief of gemengd gehoorverlies een redelijk goed lokalisatievermogen kunnen ontwikkelen mits zij op jonge leeftijd tweezijdig worden gerevalideerd. Helaas werd in deze studie geen verbetering van het geluidslokalisatievermogen gevonden na het aanpassen van de instellingen van geluidsprocessor of de lokalisatietraining.

In **hoofdstuk 8** werd de voorkeur omtrent het tijdstip van aanpassen van de geluidsprocessor geëvalueerd in 60 patiënten die werden geïmplanteerd met een BAHI. Deze studie werd opgezet

naar aanleiding van de trend om geluidsprocessoren steeds eerder na implantatie aan te meten. Volgens het huidige protocol wordt de processor drie weken postoperatief aangemeten. Redenen om een geluidsprocessor eerder aan te meten zijn het eerder kunnen opstarten van gehoorrevalidatie en het verbeteren van efficiëntie. Het aanmeten van de geluidsprocessor zou bijvoorbeeld direct postoperatief plaats kunnen vinden of gecombineerd kunnen worden met de standaard controle 1 week postoperatief. In deze prospectieve vragenlijst studie werden patiënten zowel preoperatief als postoperatief gevraagd naar het voor hun ideale tijdstip om de geluidsprocessor aan te meten. De resultaten demonstreerden dat er behoorlijk wat variatie was in de voorkeuren van patiënten. Preoperatief wilde 40%-50% de geluidsprocessor binnen één week na de operatie laten aanmeten en wilde 35%-47.5% hun geluidsprocessor omstreeks drie weken postoperatief laten aanmeten. Na de operatie daalde het aantal patiënten dat hun geluidsprocessor eerder dan de standaard drie weken wilde laten aanmeten.

Samenvattend had ongeveer de helft van de patiënten de voorkeur om de geluidsprocessor binnen één week na de operatie aan te laten meten. Om aan zowel patiënt voorkeuren als efficiëntie van de zorg tegemoet te komen, zou het aanmeten van de geluidsprocessor één week na operatie plaats kunnen vinden. Het is echter belangrijk om ons te realiseren dat de wensen van patiënten verschillen. Deze studie benadrukt het belang van het in kaart brengen van patiënt voorkeuren alvorens een nieuw behandel protocol in te voeren.

Dit proefschrift heeft de klinische en gehoor-gerelateerde kwaliteit van leven uitkomsten van de huidige botverankerde hoorimplantaten en de gouden standaard chirurgische techniek onderzocht, een nieuwe minimaal invasieve chirurgische techniek geëvalueerd en klinische uitdagingen van de huidige zorg rondom botverankerde hoorimplantaten geëxploreerd. Gezien de excellente resultaten van de huidige implantaten en chirurgische techniek, zal de aanvullende klinische waarde van nieuwe implantaten en chirurgische procedures beperkt zijn. De veiligheid en toegevoegde waarde van nieuwe producten en technieken zal daarom kritisch onderzocht moeten worden alvorens deze in de reguliere zorg te implementeren. Toekomstig onderzoek zal zich met name moeten richten op het verbeteren van klinische uitkomsten in specifieke patiënten groepen, efficiëntie van zorg en implementatie van patiëntgerichte zorg. Op deze gebieden is er nog steeds ruimte voor verdere verbetering.



APPENDICES

Research data management
List of publications
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Research data management

This thesis is based on the results of human studies, which were conducted according to the guidelines for Good Clinical Practice, ISO14155:2011, and the ethical principles stated by the Declaration of Helsinki. The local ethical committee (CMO Radboudumc) approved of all studies. None of the studies was subject to the medical research involving human subjects act (WMO).

Oticon Medical AB (Askim, Sweden) acted as a sponsor for the studies in chapter 4 and 5 and provided financial support for the studies in chapter 2-5 and chapter 8. Cochlear Bone-Anchored Solutions AB (Mölnlycke, Sweden) provided financial support for the study in chapter 7.

Prior to patient inclusion, informed consent was obtained on paper following the institutions' procedure. In several studies, patient characteristics and outcome measures were recorded on paper Case Report Forms (CRFs). Furthermore, in some studies, patients completed questionnaires on paper. Paper data, as well as relevant data obtained from EPIC, the electronic patient file system of the Radboudumc, were entered within either Castor EDC or SMART-TRIAL. Data management and, when applicable, data monitoring were also performed within these two systems. The privacy of the participants in this thesis has been warranted using random individual subject codes. This code correspondents with the code on the informed consent form and with the code on the CRF's. A pseudonymization key linked this random code with the personal data. This pseudonymization key was stored on a network drive that was only accessible to members of the project who needed access to it because of their role within the project. The pseudonymization key was stored separately from the study data. Data where converged from Castor EDC to SPSS (SPSS Inc., Chicago, Illinois, USA) and from SMART-TRIAL to SAS (Cary, NC). As for chapter 7, a part of the analyses was performed with MathWorks (Natick USA).

All primary and secondary data that was obtained for the studies described in chapter 2,3,6,7 and 8 (including raw data, data analyses, results, manuscripts and all other relevant files) have been stored on the Ear-, Nose- and Throat (ENT) department server (H:\KNOdata\Hearing_Implants\BI\Projecten). The raw data and data analyses files of the studies in chapter 4 and 5, are stored on the server of Oticon Medical AB, as they sponsored these studies. The analyzed data, manuscripts and all other relevant files of these two studies are saved on the same ENT department server as mentioned above. The informed consent forms are archived separately from the questionnaires and paper CRFs, in the department archive of the ENT department. All data will be saved for 15 years after termination of the studies. The datasets analyzed during these studies are available from the corresponding author on reasonable request.

List of publications

Published manuscripts

Hearing-related quality of life in 75 patients with a percutaneous bone conduction device
Caspers C.J.I., Nelissen R.C., Groenewoud H.J.M.M., Hol M.K.S.
Otology & Neurotology 2021; 43(3):345-351

Sound localization with bilateral bone conduction devices
Caspers C.J.I., Janssen A.M., Agterberg M.J.H., Cremers C.W.R.J., Hol M.K.S., Bosman A.J.
European Archives of Otorhinolaryngology 2021;279(4):1751-1764

A clinical evaluation of minimally invasive Ponto surgery with updated procedure package for inserting bone-anchored hearing implants
Caspers C.J.I., Kruyt I.J., Mylanus E.A.M., Hol M.K.S.
Otology & neurotology 2021;42(8):1192-1200

Patient preferences in sound processor loading time after BAHI surgery
Caspers C.J.I., Kruyt I.J. *(shared first autorship),* Mylanus E.A.M., Nelissen R.C., Hol M.K.S.
Otology & neurotology 2020;41(7):934-939

The efficacy of bone-anchored hearing implant surgery in children: a systematic review
Kruyt I.J., Bakkum K.H.E., Caspers C.J.I., Hol M.K.S.
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Six-month clinical outcomes for bone-anchored hearing implants: comparison between minimally invasive Ponto surgery and the linear incision technique with tissue preservation
Caspers C.J.I., Kruyt I.J., Mylanus E.A.M., Hol M.K.S.
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Caspers C.J.I., Dronkers E.A.C., Monserez D., Wieringa M.H., Baatenburg de Jong R.J., Hardillo J.A.U.
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Vijverberg M.A., Caspers C.J.I., Kruyt I.J., Wasmann J.W., Bosman A.J., Mylanus E.A.M., Hol M.K.S.
Otology & neurotology 2019;40(5):689-691.

Manuscripts under review

Long-term clinical outcomes of percutaneous implants for bone conduction devices: five-year evaluation of different implant designs and surgical techniques
Caspers C.J.I., Vijverberg M.A. *(shared first authorship)*, Kruyt I.J., Mylanus E.A.M., Hol M.K.S.
Clinical Otolaryngology

Submitted manuscripts

Long-term follow-up of a wide-diameter bone anchored hearing implant: 10-year experience on stability, survival, and tolerability of an implant-abutment combination
Teunissen E.M., Caspers C.J.I., Vijverberg M.A., Mylanus E.A.M., Hol M.K.S.
Otology & Neurotology

Dankwoord

Na jaren van bloed, zweet, tranen en geluk, is mijn proefschrift af en is het tijd om met mijn opgedane schrijfervaring de kers op de taart te creëren, het dankwoord. Ik wil hierin een aantal mensen bedanken, want niet alleen mijn bloed, zweet, tranen en geluk zijn verwerkt in dit proefschrift, maar (in meer of mindere mate) ook die van anderen.

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Arno en Martijn, na vele warme uren in de onderzoekstrailer (gelukkig was er airco) en na weken van data-analyse, hebben we het richting horen project, mede dankzij Katharina, tot een succesvol einde gebracht. Bedankt voor jullie kritische blik en doorzettingsvermogen bij dit project.

Dit proefschrift had nooit tot stand kunnen komen zonder de bereidheid van patiënten om deel te nemen aan wetenschappelijk onderzoek. Bij deze wil ik dan ook alle participerende patiënten bedanken voor hun deelname. Daarnaast wil ik alle coauteurs bedanken die een bijdrage hebben geleverd aan de artikelen in dit proefschrift. Hartelijk dank voor jullie waardevolle feedback.

De manuscriptcommissie. Dank voor de tijd en moeite die jullie hebben gestoken in het lezen en beoordelen van mijn proefschrift.

Staf van de afdeling Keel-, Neus-, en Oorheelkunde van het Radboudumc, in het bijzonder prof. dr. Marres en dr. van den Hoogen. Wat is onze afdeling toch een prettige plek om te werken. Bedankt voor het creëren van dit inspirerende en plezierige opleidingsklimaat.

De maatschap KNO van het Rijnstate Ziekenhuis. Wat heb ik ontzettend veel geleerd in de periode dat ik bij jullie werkzaam was. Ik heb het gigantisch naar mijn zin gehad. De tijd vloog voorbij.

Lieve collega AIOS en onderzoekers, wat een toppers zijn jullie! Samen werken is super, maar daarna is het helemaal feest. De talloze panini lunches inclusief enorme after-panini dip, heel lang koffie drinken na de overdracht, je frustraties uiten tegen een kamergenoot met een noise-cancelling head phone, de plotse liefde voor planten, vrijdagmiddag borrels in Annie, krokodillen, assistenten weekenden, kno-vergaderingen, skireizen en noem maar op. Wat een gezelligheid. Jullie hebben de overgang naar het oosten een stuk milder gemaakt.

Lieve Cindy en Ineke, mijn jaar(club)genoten en paranimfen. Wat bof ik dat ik zoveel onderzoeks- en opleidingsjaren met zulke leuke meiden mag doorbrengen. Cin, na een hele week samen in de mini-hotelkamer in Kopenhagen, wist ik dat het wel goed zou komen. Echt super om zo'n tof congres-maatje te hebben. Ien, jij sprankelt van enthousiasme, bent altijd op de hoogte van écht alles maar kan ook goed luisteren. Fijn om lief en leed met jullie te kunnen delen. Ik ben heel blij dat jullie mij bijstaan tijdens mijn verdediging.

De Serieclub: Emma, Hedwig, Jasper, Bas en Annebeth. Ik kijk altijd uit naar onze wekelijkse serie- en eetavond: het vele lachen, het ontzettende lekkere eten, de verkleedavonden bij de finale aflevering, de zelf gebrouwen limoncello (iets te sterk), het commentaar op de series en de uitputtende traileravonden (dit laatste iets minder). Laten we dit nog héél lang blijven doen.

Al mijn lieve vriendinnen uit het westen van het land: SSGW (ik ga deze afkorting niet voluit schrijven), Oud St. Sorlin (ook al ben ik daar nooit geweest), de Druifjes (wanneer gaan we over op rozijnen?) en anderen die niet passen binnen een van deze groepen. Langdurige vriendschappen zijn iets bijzonders, helemaal als ze blijven bestaan ondanks een behoorlijke reisafstand. Wat fijn dat jullie mijn vriendinnen zijn.

Lieve Alis, Özge en Fleur. Ik weet nog hoe jullie reageerden op mijn emigratie richting het Oosten. Totale paniek. Ondanks mijn emigratie zijn we er nog steeds voor elkaar door dik en dun. Dit jaar zijn we tien jaar vriendinnen en ik ben enorm blij met onze vriendschap. Ik kijk er naar uit alle mooie dingen met jullie te vieren die komen gaan.

Lieve Brent en Boyd, mijn broertjes. We zijn alle drie enorm verschillend, maar creativiteit en humor is wat ons bindt. Als kinderen maakten we samen al films en toneelvoorstellingen en als de juiste gelegenheid zich voor doet, doen we dat weer. Het enige verschil is dat ik jullie vroeger nog kon verkleden als meisje, maar jullie (je) nu niks meer van mij aantrekken. Sanne, ik ben blij dat jij onderdeel bent van onze familie. Je Limburgse gezelligheid, heerlijke taarten en liefde voor spelletjes zijn echt een aanwinst.

Lieve papa en mama, jullie hebben mij op laten groeien in een vrije en open omgeving. Niets was gek en ik zou alles kunnen bereiken, als ik er maar mijn best voor deed. Dat is een hele goede basis om je leven mee te beginnen. Ik kan altijd bij jullie terecht en als er echt een probleem is dan vechten jullie beiden als een tijger om het op te lossen. Bedankt voor jullie steun, vertrouwen en luisterende oren.

Lieve Jeroen, of je nou hier bent, in een iglo op Lapland of ergens rondvliegt in de Southern States, ik weet dat je er altijd voor me bent. Jouw rotsvaste vertrouwen in mij ervaar ik nog steeds als iets heel bijzonders. Dank voor je eeuwige geduld, het luisteren naar mijn presentaties, corrigeren van mijn uitspraak (abutment) en doorlezen van manuscripten, maar bovenal bedankt voor je Hakuna Matata mentaliteit. Nadat ik dit proefschrift heb afgerond, is mijn volgende levensdoel het leren beheersen van deze mentaliteit, dat wordt weer een meer jaren project waarbij ik je hulp goed kan gebruiken!

Curriculum vitae

Coosje Caspers werd op 15 september 1990 geboren te Roelofarendsveen, alwaar de huisarts dwars door de kermisoptocht heen moest rijden om Coosje ter wereld te brengen. Op 3-jarige leeftijd verhuisde zij naar Oude Wetering, een dorp verderop, waar zij haar verdere jeugd heeft doorgebracht met haar ouders en twee jongere broertjes. Na afronding van het Gymnasium op het Stedelijk Gymnasium te Leiden en een korte bevlieging in de vorm van een studie communicatiewetenschap, bezocht zij een introductiedag van de studie Geneeskunde. Na een korte les anatomie op de snijzaal was Coosje verkocht, ze ging Geneeskunde studeren in Rotterdam. De liefde voor anatomie bleef; tijdens haar studie werkte ze op de snijzaal en gaf zij lessen anatomie aan geneeskunde studenten. Gezien haar interesse voor hoofd-hals anatomie en het hieraan gerelateerde vak Keel-, Neus- en Oorheelkunde, besloot Coosje, na verschillende reizen door Zuidoost Azië en Zuid-Amerika, een coschap KNO in Yogyakarta Indonesië te volgen. Na het afronden van een oudste coschap KNO in het Erasmus MC te Rotterdam en een keuze coschap KNO in het Albert Schweitzer Ziekenhuis te Dordrecht, behaalde zij in september 2016 het artsexamen aan de Erasmus Universiteit te Rotterdam. Na haar afstuderen ging Coosje als ANIOS KNO aan de slag in het Albert Schweitzer Ziekenhuis te Dordrecht. Hierna werd zij aangenomen op de afdeling KNO van het Radboudumc te Nijmegen alwaar zij eerst werkte als ANIOS en vanaf november 2017 startte met haar promotietraject naar botverankerde hoorimplantaten. Vanaf april 2020 begon Coosje met de opleiding tot KNO-arts, welke zij tot nu toe deels in het Radboudumc te Nijmegen en deels in het Rijnstate ziekenhuis te Arnhem volgde. Ten tijde van de verdediging van dit proefschrift bevindt Coosje zich aan het begin van het derde jaar van haar opleiding tot KNO-arts.

PhD portfolio

Name PhD student:	*C.J.I. Caspers*	**PhD period:**	*1-11-2017/01-03-2022*
Department:	*Otorhinolaryngology*	**Promotors:**	*Prof. dr. M.K.S. Hol* *Prof. dr. E.A.M. Mylanus*
Graduate school:	*Donders graduate school for cognitive neurosciences*	**Co-promotor:**	*Dr. ir. A.J. Bosman*

COURSES AND WORKSHOPS	**Year(s)**	**ECTS**
Radboudumc introduction day	2016	0.50
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK)	2017	1.50
Graduate school introduction day	2018	0.50
Scientific writing	2018	3.00
Audiometry and audiology course	2018	2.00
Statistiek voor promovendi met SPSS	2018	2.00
Basic didactic skills	2019	0.60
Art of presenting science	2019	1.50
Scientific integrity course	2019	1.50

SEMINARS AND LECTURES	**Year(s)**	**ECTS**
Medical-clinical education and lectures at the otorhinolaryngoly department	2017-2022	2.00
OOR-ON seminar	2017-2018	0.20
Henry Wallman prize seminar (Gothenburg, Sweden)	2018	0.20
Cochlear BAHA masterclass	2018	0.20
Radboud Research Round Sensory Disorders, Radboudumc – *1 oral presentation*	2020	0.35

(INTER)NATIONAL SYMPOSIA & CONGRESSES	**Year(s)**	**ECTS**
Biannual meetings of Dutch ENT-society – *1 oral, 1 poster presentation*	2017-2021	3.50
EAONO conference (Copenhagen, Denmark) – *2 oral, 1 poster presentation*	2018	1.75
KNO onderwijsdag: wetenschappelijke integriteit	2018	0.25
CI conference (Antwerp, Belgium) – *1 oral presentation*	2018	0.50
Politzer conference (Warschaw, Poland) – *2 oral presentations*	2019	1.75
OSSEO conference (Miami, USA) – *1 oral, 1 poster presentation*	2019	1.50

TEACHING AND SUPERVISION	**Year(s)**	**ECTS**
Teaching 'transferable skills' to master students medicine	2017-2018	1.0
Supervision of research project student Medicine	2017-2019	2.5
Reviewer Otology & Neurotology	2021	0.1
Reviewer Journal of the American Acadamy of Audiology	2022	0.1

Other	**Year(s)**	**ECTS**
Working visit to Chalmers university (Gothenburg, Sweden)	2018	0.75
Organizing steering committee meetings with funders	2017-2020	6.00

Total	**35.75**