DEVELOPMENT OF MINIMALLY INVASIVE SURGICAL TECHNIQUES FOR PERCUTANEOUS BONE CONDUCTION DEVICES

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DEVELOPMENT OF MINIMALLY INVASIVE SURGICAL TECHNIQUES FOR PERCUTANEOUS BONE CONDUCTION DEVICES

Ontwikkeling van minimaal invasieve chirurgische technieken voor percutane botverankerde hoortoestellen

(met een samenvatting in het Nederlands)

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Je gaat het pas zien als je het door hebt

Johan Cruijff

CONTENTS

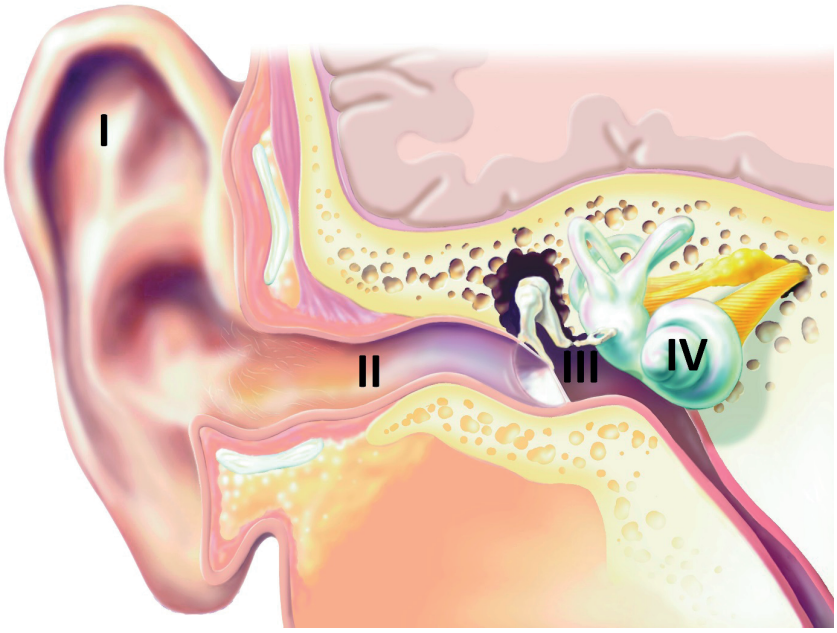
1

INTRODUCTION

The importance of the sense of hearing in experiencing the world was already described in the Classical period in Ancient Greece. The Greek philosopher Aristoteles (384–322 BC) described hearing in his well-known work *De Anima* as one of our senses which are relevant to explore the world as human being. This implicates the impact of hearing loss on multiple domains in our daily life. The World Health Organization estimates that around 466 million people have disabling hearing loss.[1] A disabling hearing loss has a significantly functional, emotional and social impact.[1] The magnitude and impact of the problem (disease burden) highlights the relevance of exploring and optimizing solutions in hearing rehabilitation.

First of all, it is essential to consider the principle of hearing. The human ear is divided in an outer ear, middle ear and inner ear (Figure 1). The outer ear consist of the pinna (auricle) and external auditory canal. The middle ear contains the tympanic membrane and the tympanic space with the ossicular chain. This ossicular chain are three connected bones: the malleus, incus and stapes (from lateral to medial). The inner ear contains the bony labyrinth consisting of the auditory sensory organ (cochlea) and the vestibulum with the three semicircular canals (organ of equilibrium). The structure of the cochlea is a spiral channel which is dived by two membranes (basilar membrane and Reissner's membrane) into three compartiments: scala vestibuli, scala tympani and scala media. The scala vestibuli is communicating with the oval window and the scala tympani with the round window.

Figure 1. The anatomy of the ear. I Outer ear. II Externa auditory canal. III Middle ear. IV Inner ear. Images reproduced by kind permission of Oticon Medical AB ©.



In a normal hearing situation, the route of hearing is mainly by air conduction. Sound vibration are conducted (and enhanced to some degree) respectively through the external auditory canal, tympanic membrane and ossicular chain. The mobile stapes footplate covers the oval window of the cochlea. As a result, sound vibrations will lead here to movement of fluid in the cochlea, allowed by the oval and round window. This fluid movement stimulates the organ of Corti leading to action potentials of the acoustic nerves and excitation of the auditory nerve pathways.

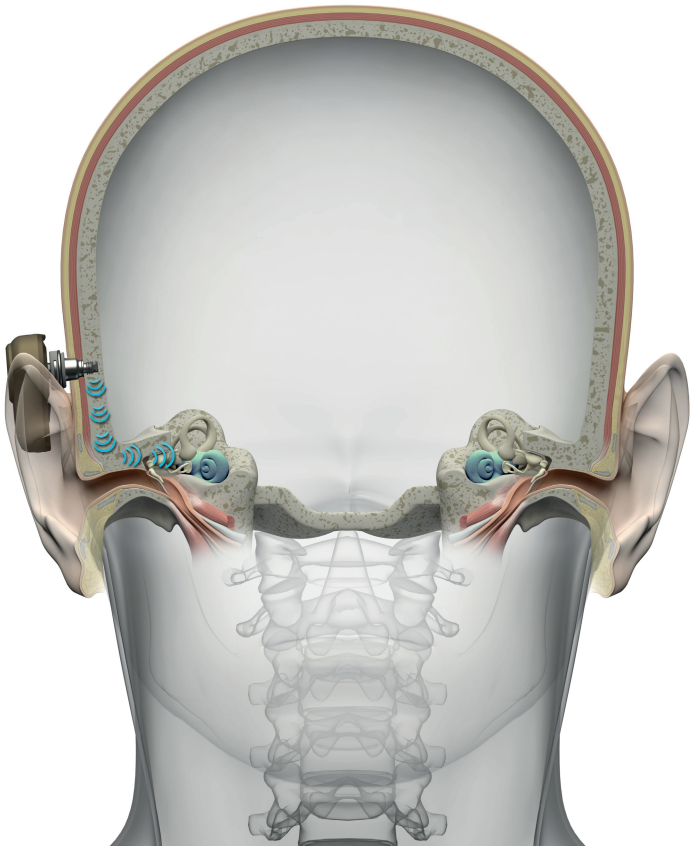
Based on the anatomy and physiology of hearing, hearing loss can be divided broadly in conductive or sensorineurinal hearing loss (SNHL). In conductive hearing loss, there is a problem in the conduction of the sound vibration towards the cochlea. This can be caused by pathology in the outer and middle ear, for example obstructing cerumen, ear drum perforation, otitis media, ossicular chain disruptions and aural atresia/microtia. If hearing loss is caused by pathology of cochlea and/or retro-cochlear structures (i.e. nervus vestibulocochlearis or further in the auditive neural pathways), this is defined as SNHL.

Examples are presbyacusis and vestibular schwannoma. Some patients have both types of hearing loss, which is described as mixed hearing loss.

As mentioned, in a normal hearing situation, the route of hearing is by air conduction. Nevertheless, bone conduction hearing is a relevant alternative route for hearing. The principle of bone conduction hearing is based on transmission of vibrations through the skull to the cochlea and surrounding bone. Starting in the beginning of the twentieth century with the theories from Krainz[2] and Herzog[3], nowadays, several pathways are proposed for bone conduction hearing.[4,5] These comprise cochlear fluid inertia, compression of the cochlear walls and pressure exchanges exerted via cerebrospinal fluid.[4,5] Also, a factor could be the vibration of the outer and middle ear through the skull which will then reach the cochlea.[5]

This principle of bone conduction hearing was the fundament for development of bone conduction devices (BCDs) as an important form of hearing rehabilitation in patients. In 1977, Tjellström was the first otorhinolaryngologist to successfully implant a BCD.[6] A BCD consists of a titanium implant which is placed retro-auricularly in the temporal bone. This is mounted with a skin-penetrating abutment. A sound processor can be attached to this abutment. The vibrations of this processor by sound waves will be transferred via the abutment/implant to the skull (Figure 2). Current guidelines state that treatment with a BCD is indicated in patients with uni- and bilateral conductive or mixed hearing loss, with an intolerance or inability to wear conventional hearing aids,[6-8] or in patients with single-sided deafness[9].

Figure 2. Schematic example of a percutaneous bone conduction device. Images reproduced by kind permission of Oticon Medical AB ©.



BCD surgery is considered a safe procedure with low risk of complications[10]. Soft tissue problems including peri-abutment inflammation (often graded by the IPS[11] or the Holgers Index[12]), skin thickening and tissue overgrowth do occur in a significant number of patients.[10,12,13] Other complications are numbness and pain at the implant site, post-operative wound dehiscence or skin necrosis and implant extrusion.[10,13] In the last decades, the dynamic research field of BCDs has been inspiring researchers worldwide to further progress for better post-operative outcomes. These improvements are focussing on the one hand on further development of implant and abutment designs. Relevant examples are the hydroxyapatite layer of the BIA400 from Cochlear (Mölnlycke, Sweden)[14,15] and the increased threaded titanium surface along the full length of the implant of the Ponto Wide from Oticon

Medical AB (Askim, Sweden)[16,17]. On the other hand, there is an important focus on the advancement of the surgical technique.

The first implantation technique used by Tjellström was a two-staged procedure. The implant was placed in the temporal bone during the first stage.[6] The second stage, twelve weeks later, consisted of the placement of the skin-penetrating abutment. This changed in the adult population to a one-staged procedure.[18,19] Also, within this one-staged procedure, the surgical technique has been evolving. Initially, subcutaneous tissue was removed in an attempt to reduce friction skin movements around the abutment. The rationale was that reduction of mobility between implant and skin would lead to less (adverse) skin reactions and other soft tissue related problems. Various surgical techniques have been developed, which started with the free retro-auricular full-thickness skin graft[20] and later on the pedicled grafts[21]. In the following years, to further reduce soft tissue problems, the dermatome technique and linear incision technique with tissue reduction (LITT-R) were introduced.[8,22] The dermatome technique was developed to standardize the pedicled flap technique and make a thinner skin graft. A specific Baha dermatome is used in order to create a skin graft without hair follicles, which stays attached to the skin on one side. There is removal of all soft tissue beneath with the formation of a gradual slope down to the implant site. The periosteum remains intact with exception of the location of insertion of the implant.[23,24]. In the LITT-R, a longitudinal incision of about 30-40 mm (depending on skin thickness) posterosuperiorly to the ear canal is made. The periosteum is visualized and mobilized after sharp dissection of the subcutaneous tissue. Subsequently, the implant is placed and subcutaneous tissue will be resected over a range of approximately 2 cm around the incision. Additionally, the remaining periosteum is removed. [25]

In the previous literature, studies reporting about the dermatome technique showed an overall higher rate of skin problems compared to studies regarding the linear incision technique. Nevertheless, variability in methodology, duration of follow-up and variability in approaches in the surgical techniques among these studies may influence the rate of post-operative soft-tissue problems.[22] More rigorous support of the superiority of the LITT-R can be provided by directly comparing the dermatome and LITT-R which will be described in *Chapter 2* of this thesis. Based on less skin complications and its procedural simplicity, the LITT-R became more popular.[22,25]. Within this LITT-R, the remaining topic to address was the

placement of the implant inside the line of incision or outside the line of incision. It was hypothesized that placing the implant outside the incision would lead to scarcely traumatized skin with reduction of inflammatory complications.[26] *Chapter 3* will compare those approaches within the LITT-R in a historical cohort study.

Last decade, the modifications in the surgical procedures for placement of the percutaneous BCD are based on the principle of less invasive surgery. The LITT-R evolved to the linear incision technique with tissue preservation (LITT-P) (Figure 3) .[27] Studies did show improved outcomes, including shorter surgical time, more satisfactory cosmetic results and less numbness when using the LITT-P technique.[14,28-33] *Chapter 4* will focus on evaluation of the LITT-P compared to the LITT-R in order to substantiate the evidence[13,14,27,32-35] for similar or less soft-tissue related complications. Recently, to further decrease soft tissue reactions, the surgical technique was simplified to a minimally invasive, so-called punch-only technique.[36-39] These procedures with a punch-hole only should theoretically result in even less soft tissue trauma. Several surgeons performed this principle and described better cosmetic results and shorter surgical procedure time without noticing more soft tissue problems in comparison with the dermatome or linear incision technique.[36-39] A standardized approach including surgical kit for the punch-only technique, introduced by Oticon Medical AB (Askim, Sweden), is the Minimally Invasive Ponto Surgery (MIPS).[40] In the MIPS procedure, an incision is created with a 5-mm punch with the removal of the remaining soft tissue and periosteum in the punch hole. A cannula is inserted at the surgical site and the further drilling procedure is primarily similar to the linear incision techniques (Figure 4).[40,41]

Figure 3. Surgical steps of the LITT-P.

I) Three to four cm long linear incision down to the periosteum is made. II) The incision is opened up using a self-retaining retractor and the periosteum around the surgical site is removed. III) Guide drilling is performed. IV) If the bone thickness is sufficient, the spacer is removed to prepare for a 4 mm implant. V) The hole is widened with the countersink. VI) The implant with pre-mounted abutment is installed. VII) A hole for the abutment is made using a 5 mm biopsy punch. VIII) The skin is eased over the abutment and the incision closed. IX) A healing cap is attached to the abutment and a suitable dressing applied.

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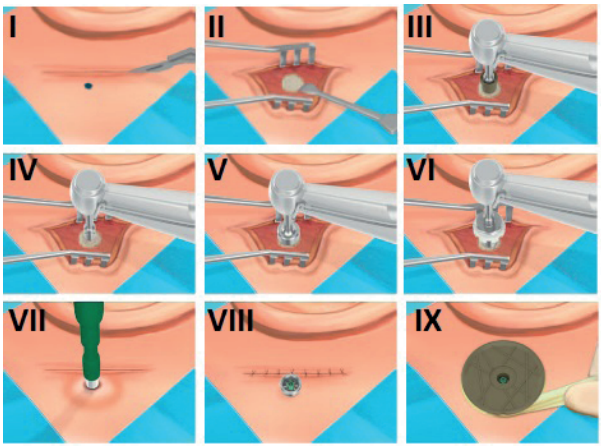

Figure 4. Surgical steps of the MIPS.

I) An incision is made using a 5 mm biopsy punch. II) A raspatorium is used to ensure that all soft tissue and periosteum are removed around the surgical site. III) The cannula is then inserted. IV) Guide drilling is performed through the cannula with the guide drill. V) The guide drill has a spacer that is removed if the bone thickness allows a 4 mm long implant. VI). The hole is thereafter widened. VII) The cannula is removed and the implant with pre-mounted abutment installation is performed through the circular incision. VIII) A healing cap is attached to the abutment and a suitable dressing applied.

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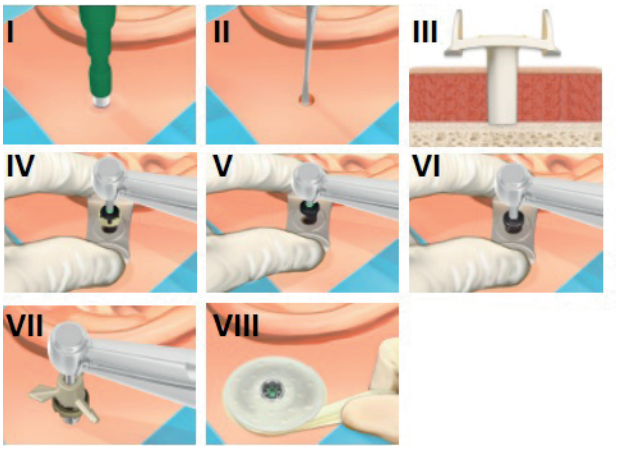

Studies comparing the MIPS technique to the LITT-P found significantly shorter surgical time with similarly favorable outcomes regarding soft tissue reactions after short-term follow-up.[39,42-46] Also, less sensibility loss[42] and better cosmetic appearance[42,43] were registered. These findings warrant long-term follow-up which is provided by the 22 months results of a randomized controlled trial comparing the MIPS with the LITT-P in *Chapter 5*. Some of the initial studies into the MIPS technique did demonstrate potentially more implant extrusions.[43,44] Recently, these possible concerns have been translated into the development of a new drill system. *Chapter 6* will show an ex-vivo experimental study evaluating this novel MONO drill system on fresh frozen, human temporal bone samples, which is the basis for a clinical evaluation to follow. Finally, it is important, also from societal perspective, to take the resources and costs into account when introducing an (alternative) surgical technique. A health economic study can be used to improve understanding of benefits, harms and costs of interventions and contribute to informed decision making. *Chapter 7* will show the first health economic costs analysis comparing the MIPS with LITT-P technique.

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2

PERCUTANEOUS BONE-ANCHORED HEARING IMPLANT SURGERY: DERMATOME VERSUS LINEAR INCISION TECHNIQUE

Ruben M. Strijbos, Steven J.H. Bom, Stefan Zwerver, Myrthe K.S. Hol.

European Archives of Otorhinolaryngology. 2017;274:109-117.

Abstract

The objective of this historical cohort study is to identify if there are differences in soft tissue reactions and skin thickening between implantation of the percutaneous bone-anchored hearing implant (BAHI) using the dermatome or linear incision technique. All adult patients who received a BAHI between August 2005 and January 2013 were selected. One surgeon performed all procedures and only the dermatome and linear incision technique were used. A total of 132 patients/implants were included and significantly more patients with risk factors were seen in the linear incision cohort. A soft tissue reaction Holgers ≥ 1 was present in 18 patients (40.9 %) in the dermatome compared to 36 patients (40.9 %) in the linear incision group. A Holgers ≥ 2 was noticed in 9 (20.5 %) respectively 19 (21.6 %) patients. Skin thickening was described in 14 (31.8 %) and 11 patients (12.5 %) in respectively the dermatome and linear incision cohort, which was a significant difference (p = 0.001). Nevertheless, therapeutic interventions were effective. In conclusion, there was no significant difference in (adverse) soft tissue reactions, however skin thickening was more present in the dermatome technique. Also, significantly more patients with risk factors were allocated to the linear incision technique. Based on these results, the linear incision is advocated as preferred technique.

Background

Since the first implantation in 1977 by Tjellström, percutaneous bone-anchored hearing implants (BAHIs) offer an appealing solution in hearing rehabilitation for patients with a conductive or mixed hearing loss[1,2] and single-sided deafness[3-6]. These devices stimulate the cochlea directly through the principle of bone conduction[1]. The ongoing developments in the field of bone conduction devices have led to a safe procedure of implantation with a lack of major complications.[7] However, depending on type of implant and abutment, surgical technique and postoperative care, soft tissue reactions are still occasionally a problem.[7-12] The Holgers' classification is most commonly used to grade these soft tissue reactions.[12]

The surgical procedure for implantation in adults is nowadays performed as an one-staged procedure.[2] Various surgical techniques have been developed, which started with the free retroauricular full-thickness skin graft[13] and later the pedicled grafts[14]. Over the years the dermatome and linear incision technique have been introduced with the goal to further minimize skin problems postoperatively[15,16]. The dermatome technique was developed to standardize the pedicled flap technique and create a thinner skin graft. A Baha dermatome is used to create a skin graft without hair follicles, which stays attached to the skin on one side. The soft tissue beneath will be removed, with the creation of a gradual slope down to the implant site. The periosteum remains intact with exception of the place of insertion of the implant.[17,18] In the linear incision technique, a longitudinal incision of about 30 mm posterosuperiorly to the ear canal is made. The periostium is exposed and mobilized after sharp dissection of the subcutaneous tissue. Subsequently, the implant is placed and subcutaneous tissue will be resected over an area of approximately 2 cm around the incision. In addition, the remaining periosteum is removed.[19] Recent studies show promising results in the context of surgical techniques with tissue preservation.[20-23]

Based on the available literature, studies reporting about the dermatome technique show an overall higher rate of skin problems compared to studies regarding the linear incision technique and nowadays this latter technique is gaining more interest as standard of care. Nevertheless, variability in set-up, follow-up and surgical techniques among these studies may influence the rate of skin complications.[16] To our knowledge, there are only two comparative studies that evaluate major postoperative complications between these two

techniques: one as part of a comparison of several techniques[24] and another with a limited follow-up without using the Holgers classification[25]. The aim of the current historical cohort study is to provide more rigorous support of the superiority of the linear incision technique by directly comparing both the dermatome and linear incision technique with subcutaneous soft tissue reduction in adults. There will be an evaluation if there are differences in the presence of soft tissue reactions, as classified by the Holgers' grading system, and skin thickening between these two techniques, alternatively performed by a single surgeon in a general, teaching hospital.

Materials and Methods

Patients

All adult patients (aged 18 years or older) who received any type of percutaneous bone-anchored hearing implant (BAHI) at one large Dutch general, teaching hospital between August 2005 and January 2013 were consecutively selected from our local Bone Implant database. Indications for a percutaneous BAHI were conductive or mixed hearing loss and single-sided deafness. Eligibility criteria were: one-staged procedure, primary placement of the implant (no previous implant removal or loss) and availability of the patient's medical chart including at least one postoperative visit at the outpatient clinic.

Surgical techniques and post-surgery protocol

Only the dermatome technique[17] and simplified linear incision technique with subcutaneous soft tissue reduction[19] were used in the selected study period. In addition, all patients were operated on by the same surgeon (S.B.). There was preoperatively screening for an increased risk of skin flap necrosis[17]. If one or more possible risk factors were present or suspected, patients were operated with the linear incision technique. Otherwise a patient underwent generally the procedure using the dermatome technique. Risk factors were high age (75 years or older), smoking, diabetes mellitus, mental retardation or cardiovascular comorbidity.[26-29]

The first postoperative visit was one week after surgery, when the healing cap and gauze with antibiotic ointment (only in the 41 first patients) or Mepilex foam (Mölynlycke Health Care, Gothenburg, Sweden; in the majority of patients) were removed. The wound was inspected

and all patients received, conform protocol in the hospital, topical therapy with fusidic acid for 2-4 weeks. Further follow-up was after three weeks, six months and twelve months and then in principle every year. Extra appointments were arranged by patients or physicians if problems arose or depending on individual needs. During each visit, there was registration of the degree of soft tissue reaction and skin thickening. If any postoperative problems occurred, i.e. skin flap necrosis, wound dehiscence or implant loss, this was also recorded. Besides, there was registration of therapeutic interventions, if applicable. End of the follow-up was defined as the last follow-up before November 2015.

Case-analysis

All data were obtained from the local database and patient's medical records of the aforementioned teaching hospital. The operative report was used to collect information about the surgical technique and implant type. Furthermore, the notes from the physical examination in all follow-up contacts by one of the physicians or residents were used to determine the presence of postoperative complications, skin thickening and soft tissue reactions.

The postoperative complications were divided in skin flap necrosis, wound dehiscence or implant loss. Skin flap necrosis was further split in minor, medium or major, which indicated respectively a non-vital skin-flap of less than 25 %, 25% to 50 % or more than 50 % of the total flap.[17] Wound dehiscence was subdivided in dehiscence without need for surgical intervention versus dehiscence which required a free skin graft. Finally, in case of implant loss there was registration of the cause.

The skin was described as low or thickened. The term skin thickening was defined as (partially) high skin around the abutment or soft tissue overgrowth. The possible therapeutic intervention was corticosteroid injection with triamcinolone acetonide, otherwise an extended abutment could be placed or eventually surgical soft tissue revision might be considered.

The soft tissue reactions were graded according to the Holgers' classification.[12] A distinction was made between soft tissue reactions in general and adverse soft tissue reactions, because of the clinical implications of the latter (i.e. indication for (topical) treatment). An adverse

soft tissue reaction was defined as a Holgers 2 or higher and a soft tissue reaction as a Holgers 1 or higher. Besides, if the Holgers notation was missing but there was notation of redness, swelling, moistness and/or granulation, this was interpreted as the presence of a soft tissue reaction. No notation of signs of inflammation in the physical examination was considered as a Holgers grade 0, i.e. the absence of soft tissue reaction.

Finally, the background characteristics gender, body-mass index, diabetes mellitus, mental retardation, smoking and cardiovascular comorbidity were registered, following recent studies focusing on identification of these comorbidities as (potential) risk factor for soft tissue reactions or implant loss.[8,30-34] Also, some characteristics may be associated with skin flap necrosis or impaired wound healing.[26-28]

Statistical analysis

A comparison of background characteristics was performed using a student's t-test if there was a normal distribution, otherwise a Mann-Withney U-test was performed. The Kolmogorov-Smirnov test was used to determine whether the criteria for normal distribution were met. The chi-square test was performed if the outcome was a proportion. In the context of the presence of skin thickening and (adverse) soft tissue reactions, there were survival curves calculated using the Kaplan-Meier method. The log-rank test was executed to identify differences between these curves. The level of significance applied was $p = 0.05$. All our analyses were performed using Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Armonk, NY; IBM Corp), version 22.0.

Results

Patients

In the period from August 2005 until January 2013, a total of 146 implants were placed. A cohort of 132 implants met the eligibility criteria, because 14 implants were excluded: 10 implants were placed in children (aged younger than 18 years) and 4 implants were no initial placement. Since none of these implants were placed bilaterally, the cohort consisted also of 132 patients. A total of 44 patients were operated using the dermatome technique with a mean age of 50.3 years (range 26-72, SD ± 12.3) and median follow-up of 40.5 months (interquartile range (IQR) 22.5-72.25). The linear incision group consisted of 88 patients with

a mean age of 59.3 years (range 22-89, SD ± 14.3) and median follow-up of 56.5 months (IQR 29.5-89.75).

All the baseline patient characteristics are summarized in table 1. As mentioned, patients were preoperatively screened for an increased risk of skin flap necrosis and underwent in general the linear incision technique if one or more possible risk factors were present. This explains the significant difference found in age (p = 0.001), diabetes mellitus (p = 0.039), cardiovascular comorbidity (p = 0.036) and smoking (p = 0.031) between the groups. Table 2 shows the surgical characteristics. In addition, only 5.5 and 6.0 mm (and no extended) abutments were used for previous generation Cochlear respectively all other implants. Moreover, significantly more previous generation implants were placed in the linear incision cohort (p = 0.033).

Table 1. Summary of the patient characteristics. * = significant difference (p < 0.05)

		Dermatome		Linear incision		P-values
		n	**%**	**n**	**%**	
Total patients/implants		44	100	88	100	
Gender	Male	20	45.5	53	60.2	0.108
	Female	24	54.5	35	39.8	
Age at surgery	Mean (years) [±SD]	50.3 [12.3]		59.3 [14.3]		***0.001****
	Range (years)	26-72		22–89		
Aetiology of hearing loss	Conductive/mixed hearing loss	34	77.3	83	94.3	
	Single-sided deafness	10	22.7	5	5.7	
Comorbidity factor	Mean body-mass index (kg/m2) [±SD]	26.9 [4.4]		27.1 [4.4]		0.816
	Diabetes mellitus	1	2.3	12	13.6	***0.039****
	Cardiovascular comorbidity	18	40.9	53	60.2	***0.036****
	Mental retardation	0	0	5	5.7	0.107
	Smoking	4	9.1	21	23.9	***0.031****

Table 2. Summary of the surgical characteristics

Characteristics		Dermatome		Linear incision	
		n	**%**	**n**	**%**
Follow-up	Median (months)	40.5		56.5	
	Interquartile range (months)	22.5-72.25		29.5-89.75	
Side	Right	23	52.3	46	52.3
	Left	21	47.7	42	47.7
Implant length	3 mm Cochlear	0	0	5	5.7
	4 mm Cochlear	36	81.8	71	80.7
	3 mm Oticon	0	0	1	1.1
	4 mm Oticon	8	18.2	11	12.5
Implant type	Previous generation Cochlear ("flange fixture")	25	56.8	66	75
	BIA300	11	25	10	11.4
	Ponto Regular	8	18.2	12	13.6
Bottom	Bone	33	75.0	63	71.6
	Dura	8	18.2	19	21.6
	Bone/dura	3	6.8	6	6.8

Postoperative complications

Skin flap necrosis was noticed only in the dermatome technique. Minor skin flap necrosis was seen in three patients (6.8 %) and medium skin flap necrosis in one patient (2.3 %). None of these cases required surgical intervention Also, no patient developed major skin flap necrosis. Dehiscence of the surgical wound was only seen in the linear incision technique. In 26 patients was registration of dehiscence without need of surgical intervention (29.5 %) and in two patients the severity required a free skin graft (2.3 %). One of these patients had multiple risk factors for impaired wound healing; the other patient had postoperative persistent blood clots in the wound because of dysregulated coagulation (which impaired closure of the dehiscence).

During complete follow-up, four implants were lost which were all previous generation implants (Cochlear flange fixture, 4 mm) and placed according to the linear incision technique. All of these implants were lost after more than six years of follow-up (74, 78, 84 and 89 months). Two implants were lost spontaneously after a distinct period with pain, one implant

was lost presumptively after a peri-implantitis and one implant was lost due to trauma. No implant was lost because of a Holgers grade 4.

Skin thickening

The presence of skin thickening was described in 14 patients (31.8 %) in the dermatome group and 11 patients (12.5 %) in the group operated using the linear incision technique. Nevertheless, soft tissue overgrowth was not recorded during the entire follow-up. The Kaplan-Meier curves including the accompanying survival graphic are shown in figure 1. These curves are showing the probability of surviving, i.e. not encountering the condition of skin thickening, in a given length of time for patients in the different cohorts. The presence of skin thickening was significantly higher in the dermatome cohort (p = 0.001). In addition, table 3 shows the therapeutic interventions in patients with skin thickening. No intervention was necessary in three patients. All other patients received triamcinolone acetonide injection and/or a higher abutment. Soft tissue reduction was performed in two patients. The therapeutic interventions were eventually effective in all cases.

Figure 1. The Kaplan-Meier analysis for skin thickening (p = 0.001).

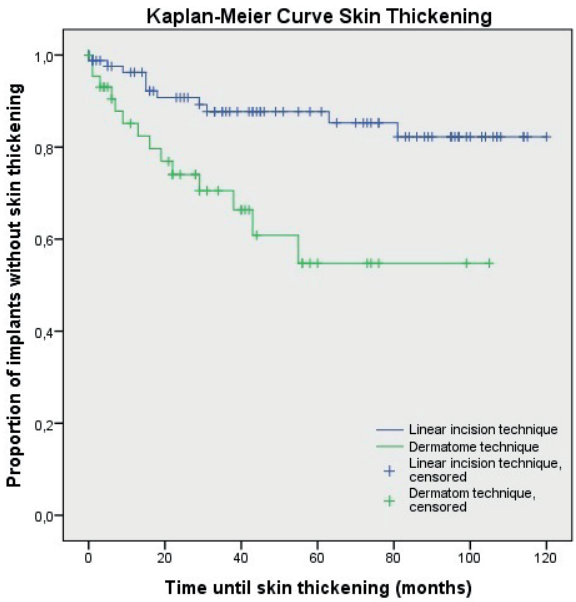


Table 3. Overview of the different therapeutic interventions for skin thickening and how often these procedures had to be performed in every patient.

		Dermatome		Linear incision	
		n	**%**	**n**	**%**
Number of patients with skin thickening		14	100	11	100
Number of triamcinolone acetonide injections	0	1	7.1	3	27.3
	1-2	5	35.7	5	45.5
	3-5	3	21.4	2	18.2
	6-10	5	35.7	1	9.1
Number of abutment changes	0	8	57.1	8	72.7
	1	6	42.9	1	9.1
	2	0	0	2	18.2
Number of soft tissue reductions	0	13	92.9	10	90.9
	1	1	7.1	0	0
	2	0	0	1	9.1

Soft tissue reactions

In the group of patients operated with the dermatome technique, a soft tissue reaction (i.e. Holgers ≥ 1) was noticed in 18 persons (40.9 %) compared to 36 persons (40.9 %) in the group of the linear incision technique. Adverse soft tissue reactions (i.e. Holgers ≥ 2) were noticed in 9 patients (20.5 %) who underwent the procedure with the dermatome. In comparison, 19 patients (21.6 %) in the group of the linear incision technique encountered an adverse soft tissue reaction. For these two outcomes measures, the Kaplan-Meier method was used to calculate survival curves (figure 2 and 3). No significant differences were found between the dermatome and linear incision technique for both the presence of soft tissue reactions (p = 0.710) and adverse soft tissue reactions (p = 0.925).

Figure 2. The Kaplan-Meier analysis for soft tissue reaction Holgers ≥ 1 (p = 0.710).

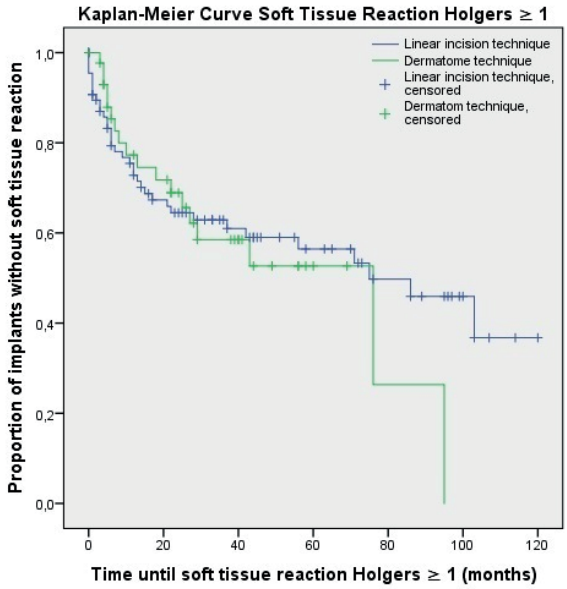
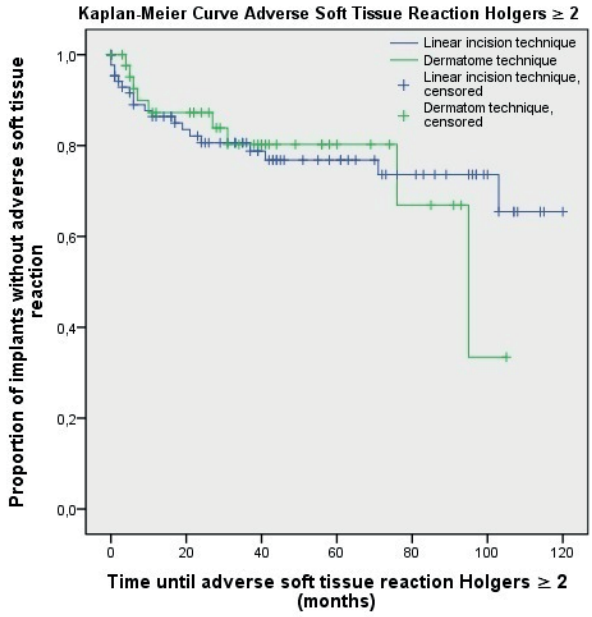


Figure 3. The Kaplan- Meier analysis for adverse soft tissue reaction Holgers ≥ 2 (p = 0.925).



Due to the aforementioned significantly higher rate of previous generation implants in the linear incision group, a statistical subanalysis was performed for the soft tissue reactions and skin thickening according to implant type (i.e. previous generation bone implants ("flange fixture") versus the more recent BIA300 and Ponto Regular implants). The percentage of implants encountering skin thickening, Holgers ≥1 and Holgers ≥2 was, respectively, 24.2, 48.4 and 28.6 % in the previous generation bone implant group. In the group of BIA300 and Ponto Regular implants these percentages were, respectively, 7.3, 24.4 and 4.9 %. A Kaplan–Meier analysis with log-rank test revealed that the difference in skin thickening (p = 0.119) and soft tissue reactions Holgers ≥1 (p = 0.120) was not significant. Nevertheless, significantly more adverse soft tissue reactions Holgers ≥2 were encountered in the previous generation implants (p = 0.020).

A subanalysis of patients without any possible risk factors for skin problems could not be performed due to a too low number of eligible patients in both cohorts for comparison.

Discussion

In this retrospective cohort study, 132 implants were studied in 132 patients with a total median follow-up time of 47.5 months (IQR 26.0–84.75). There were no statistically significant differences found in the presence of soft tissue reactions or adverse soft tissue reactions between patients who underwent surgery with the dermatome technique and patients operated with the linear incision technique in the current set up. Skin thickening was significantly more encountered in the dermatome cohort, but could be treated successfully.

Over the last decade, several developments and improvements have been made in implant types, sound processors and surgical techniques. In the field of the latter, both the dermatome and linear incision technique became popular in many centres. However, studies regarding the dermatome technique reported an overall higher rate of skin problems[35-37] compared to the linear incision technique[8,19], although methodological variability could influence these outcomes and impair adequate comparison[16]. The linear incision technique is more and more used as the preferred technique in many clinics. Moreover, several promising modifications in this surgical approach are investigated in the current literature, for example the use of minimally invasive techniques without subcutaneous tissue thinning[20-23].

Unfortunately, some of these studies use the dermatome technique as control cohort.[20,21]. Nevertheless, to our knowledge, this is the first large-scale historical cohort study that actually directly compares patients operated with the dermatome and the linear incision technique with soft tissue reduction in the context of skin problems using the Holgers grading system consequently. It will contribute to more solid support of the linear incision technique as preferred surgical technique in the bone-anchored hearing implant surgery.

Furthermore, this study reveals a relatively long follow-up with a median of almost 4 years. The presence of skin problems is concentrated in the first years postoperatively, thus in most implants this period is covered. In addition, only four (2.9 %) of all identified implants in adults placed during the study period had to be excluded. The combination of this very low exclusion rate and a presence of (adverse) soft tissue reaction that is comparable with other studies, though for dermatome technique somewhat lower[16], suggests a representative sample.

Moreover, both surgical techniques were performed by the same surgeon, so differences in other aspects of the surgical and perioperative approaches could be minimized to prevent possible confounding. In addition, this surgeon himself saw in general all patients during their complete follow-up. Regarding the subjective interpretation of most of the outcome measures, this small variability in observers is rather advantageous.

Nevertheless, the allocation of patients was not randomized. As stated, patients with one or more (suspected) risk factors for skin problems underwent implantation with the linear incision technique in most cases. Therefore, significantly more patients with risk factors (i.e. higher age, diabetes mellitus, cardiovascular disease and smoking) were seen in that cohort. This selection bias may have led to an underestimation of the skin problems in the dermatome cohort and overestimation in the linear incision group. Hence, there could have been a difference in (adverse) soft tissue reaction if there would have been a more equal distribution.

In addition, 91 of 132 included implants (68.9 %) were previous generation implants from Cochlear (“flange fixture”). This is a limitation of the study, because ongoing advances in implants and abutments have led to less skin reactions in the current types[38], with most recently, for example, the introduction and investigation of abutments with a hydroxyapatite

coating[39,40]. Our local Bone Implant database revealed that adverse soft tissue reactions Holgers ≥2 were significantly more encountered in the cohort with previous generation implants ("flange fixture") compared to the newer implant abutments, i.e. Ponto Regular and BIA300. Although not significant, there was clearly a trend of less soft tissue reactions Holgers ≥1 and skin thickening in patients with these newer implants. The significantly higher rate of previous generation implants in the linear incision cohort contributes to the presumption that skin problems would have been noticed less frequently in this group, if the rate of current implant types was comparable with the dermatome group. Consequently, there may have been a difference in (adverse) soft tissue reaction and an even greater difference in presence of skin thickening.

An additional point of discussion is the missing of Holgers classification in, however, a substantial minority, of the follow-up contacts. In these cases, only a description of the skin surrounding the titanium skin-penetrating abutment was available and, as comprehensively described in Materials and Methods, assumptions were made about the presence or absence of a soft tissue reaction. Moreover, there does not exist a uniform grading system of skin thickening in the international literature yet. Nevertheless, as compared to other studies, the grade of skin thickening noticed was relatively mild. There was no overgrowth of skin reported and revision surgery was performed in only 2 patients (one from each group).[8,11,16,35,36]

As to speculate on possible causes for the higher rate of skin thickening following the dermatome technique, two factors might be of interest. First, the periost is preserved in the dermatome technique whereas removed in the linear incision approach, which might result in different mobility of the skin surrounding the abutment. Second, although both techniques make use of subcutaneous soft tissue reduction, the technical performance of this reduction (i.e. manually or mechanically) might be of influence in postoperative outcomes. In other words, skin reduction in the linear incision technique is less invasive and for that reason causes less traumatized skin, which would result in a lower percentage of patients with skin thickening.

In conclusion, no significant difference was found in the presence of soft tissue reactions and adverse soft tissue reactions (i.e. Holgers grade 2 or higher) between the dermatome and linear incision technique. However, the allocation of significantly more patients with risk

factors and patients with previous generation implants to the linear incision cohort may have caused an underestimation of the difference between these two techniques. Skin thickening was significantly more seen in patients operated with the dermatome technique, which was treated successfully in all cases. Although items like aesthetic appearance, numbness, surgery time and healing time are not addressed in the current study, the linear incision technique should be preferred over the dermatome technique, based on the combination of no difference or possibly more (adverse) soft tissue reactions in the dermatome cohort and a significantly higher rate of skin thickening in this group.

As a matter of fact, this is the first historical cohort study directly comparing two widely used surgical techniques for BAHI implantation in such a large group of patients with a long-term follow-up. It adds knowledge for clinical practice and research and also contributes as a useful reference work. This study shows the strength of the linear incision in minimizing postoperative skin problems. Such well-founded evidence is of great importance, especially in the dynamic field of ongoing developments in bone-anchored hearing implants and surgical implantation techniques.

Acknowledgement

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3

PERCUTANEOUS BONE-ANCHORED HEARING IMPLANT SURGERY: INSIDE OR OUTSIDE THE LINE OF INCISION?

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European Archives of Otorhinolaryngology. 2016;273:3713-3722.

Abstract

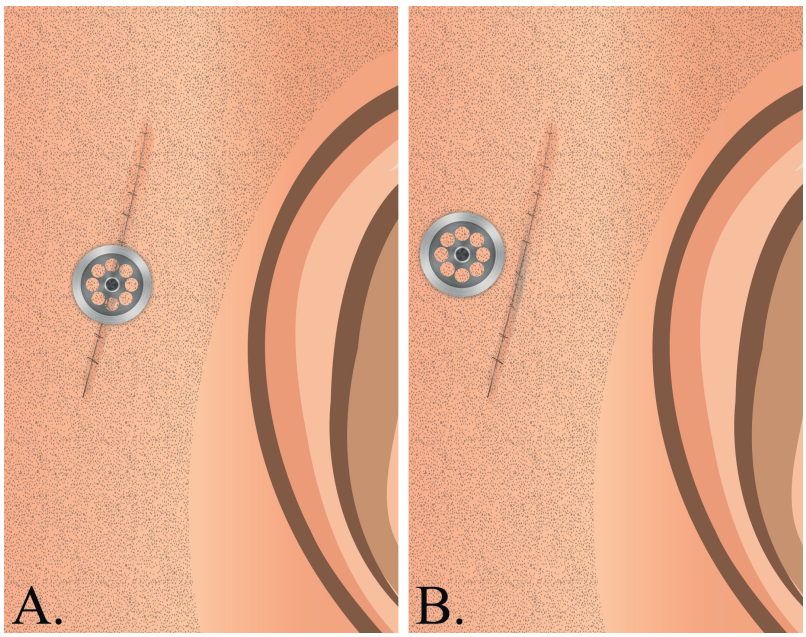
The objective of this historical cohort study was to compare soft tissue reactions in adults after bone-anchored hearing implant (BAHI) surgery when the percutaneous implant is placed inside or outside the line of incision. All adult patients who received a percutaneous BAHI between 1 January 2010 and 31 January 2014 in our tertiary referral centre were identified. Patients were selected if operated by two surgeons, who perform the same standardised linear incision technique with one of them placing the implant outside the incision while the other prefers placement inside the line of incision. A total of 202 patients and 211 implants were included in the case analysis. The results showed the registration of a soft tissue reaction Holgers ≥1 in 47 implants (49.0 %) placed outside the incision compared to 70 implants (60.9 %) which were placed inside the line of incision. An adverse soft tissue reaction, Holgers ≥2, was noticed in 17 implants (17.7 %), respectively, 20 implants (17.4 %). No significant differences were found between the two groups for both the presence of soft tissue reactions Holgers ≥1 ($p = 0.322$) and a Holgers score ≥2 ($p = 0.951$). During the follow-up three implants were lost (1.4 %) and in 18 of 211 implants one or multiple revisions were performed (8.5 %). In conclusion, this study did not show any differences in the presence of postsurgical (adverse) soft tissue reactions between placement of the percutaneous BAHI inside or outside the line of incision.

Introduction

Since Tjellström introduced the percutaneous bone-anchored hearing implant (BAHI) for bone conduction hearing in 1977; two hundred thousand patients have already benefited from this hearing rehabilitation option. A bone conduction device (BCD) is a successful treatment for patients with both conductive and mixed hearing loss[1,2] and single-sided deafness[3-6]. The procedure for implantation of osseointegrated implants is safe with a lack of major complications.[7,8] Nevertheless, adverse soft tissue reactions around the titanium skin-penetrating implant are still a frequent problem, leading to discomfort for the patient and increased visits to the outpatient clinic. A small percentage of these patients will suffer from recurrent soft tissue problems, soft tissue overgrowth or even implant loss.[7-11] The classification proposed by Holgers et al. in 1988 is the most commonly used grading system for these postsurgical skin reactions.[9]

Over the years there have been various surgical techniques used for bone-anchored hearing implantation to prevent and minimise skin problems postoperatively, like the free retro-auricular full-thickness skin graft, pedicled grafts, dermatome technique and the linear incision technique.[12,13] The linear incision technique has become most popular because of its procedural simplicity and association with less skin complications compared to the other techniques.[13,14] This technique has become even more popular nowadays with so-called soft tissue preservation, in which after the linear incision no reduction of subcutaneous tissue is performed. The remaining item to address is the implant placement when using the linear incision technique, i.e. the implant inside the line of incision or the implant outside the line of incision (Figure 1). It is suggested that when placing the implant outside of the incision, it would be surrounded by scarcely traumatised skin, reducing the inflammatory reaction occurring around it and leading to less skin complications.[15]

Figure 1. A. Linear incision technique with placement of the percutaneous abutment inside the line of incision. B. Linear incision technique with placement of the percutaneous abutment outside the line of incision.



The aim of the current study is to identify if there is a difference in postsurgical soft tissue reactions, as classified by the Holgers grading system, in adults when the percutaneous titanium implant is placed inside or outside the line of incision.

Methods

Patients

For this cohort study, all adult patients (aged 18 years or older) who received any type of percutaneous BAHI at our clinic between 1 January 2010 and 31 January 2014 were identified from our Bone Implant database. Patients operated by two surgeons, A and B, were selected. Both surgeons use the same standardised linear incision technique; they were trained and work in the same centre. Surgeon A places the implant outside the line of incision on a consistent basis, while the other surgeon B consistently uses the technique with placement of the implant inside the line of incision.

Eligibility criteria were: one staged procedure with tissue reduction, initial placement of the implant (no previous implant loss or removal) and availability of the medical record including at least one postoperative visit at our outpatient clinic.

Surgical techniques and post-surgery protocol

In the selected study period the simplified linear incision technique with subcutaneous soft tissue reduction was consistently used.[14] In this procedure, a longitudinal incision of approximately 30 mm is made with the optimal site of implantation being approximately 50 to 55 mm posterosuperiorly to the ear canal. The next step is the exposure and mobilisation of the periosteum after sharp dissection of the subcutaneous tissue. Subsequently, the implant is placed and there will be resection of subcutaneous tissue over an area of approximately 2 cm around the incision. The remaining periosteum will be removed. In the final step of the surgical procedure, surgeon A punches the skin next to the incision while surgeon B punches the skin in the line of incision, consequently placing the implant outside or inside the line of incision, respectively .

The first postoperative visit was a week after surgery, when the healing cap and gauze with antibiotic ointment were removed, followed by an inspection of the incision. All patients received topical therapy with hydrocortison/oxytetracycline/polymyxine B for 2 weeks during the first postoperative visit. This visit was followed by an appointment for fitting of the sound processor after 3-6 weeks. Further follow-up was in general after 3 and after 12 months. Extra visits could be initiated by physicians or patients depending on arising problems or individual needs. In addition, some patients visited the outpatient clinic more often because they participated in clinical trials[16,17]. At each visit, there was registration of the degree of skin reaction, using the Holgers grading system[9], and therapeutic intervention if applicable.

Case analysis

Data were obtained from our Bone Implant database and patients medical charts. Information about incision technique, surgeon and implant type was collected. Unless otherwise described in the operative report, it was registered that surgeon A placed the implant outside the incision line and surgeon B placed the implant inside the line of incision.

All follow-up visits by one of our physicians, residents or specialised nurses were included in the analysis; consultation by telephone was not included. The notes from the physical examination were used to determine the presence and timing of a soft tissue reaction. A Holgers classification 2 or higher was registered as an adverse soft tissue reaction and a Holgers classification of 1 or higher was classified as a soft tissue reaction. The reason for this distinction was because of the clinical consequences of the adverse soft tissue reaction, namely an indication for (local) treatment. Additionally, if the Holgers notation was missing but there was notation of any redness, swelling, moistness and/or granulation around the titanium skin-penetrating implant in the medical record, this was still interpreted as presence of a soft tissue reaction. A soft tissue reaction was considered not present in case of a Holgers score 0 or no notation of inflammation of the skin in the notes of the physical examination. A lack of description about the tissue surrounding the implant in the notes of a follow-up contact was considered as missing data.

Therapeutic interventions for skin problems were recorded per visit. Conforming to the general protocol in our hospital, all patients received topical therapy with hydrocortison/oxytetracycline/polymyxine B during the first weeks post-surgery. This topical therapy was therefore not considered as a therapeutic intervention in our study. Alternative therapeutic interventions were distinguished: topical antibiotic ointment, healing cap replacement and revision surgery (change of the abutment and/or soft tissue revision). Implant loss was registered as well.

Finally, the background characteristics mental retardation, dermatological disease and diabetes mellitus were registered, because recent studies focus on identification of these comorbidities as possible risk factors in the context of soft tissue reactions after BAHI surgery.[7,18-20] If there were no notes for these conditions in the medical chart or any correspondence within the chart of the patient, this comorbidity factor was considered absent. End of the follow-up was defined as the last visit before March 2015.

Statistical analysis

The presence of postsurgical soft tissue reaction during follow-up in the two groups was analysed using Kaplan–Meier curves. A log-rank test was performed to determine differences in soft tissue reaction between the cohorts. The level of significance applied was $p = 0.05$. All

analyses were performed using Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Armonk, NY; IBM Corp), version 20.0.

Results

Patients

A total of 202 patients and 211 implants could be included in the cohort in the period from 1 January 2010 until 31 January 2014. Surgeon A placed the implants consistently outside the line of incision and surgeon B placed the implants consistently inside the line of incision. Three exceptions were retrieved, in which the purpose always was to place the implant inside the line of incision. However, after closure, due to anatomical variation, it turned out the implant was outside the line of incision. From all implants, 96 BAHIs were placed outside the line of incision. The mean age in this group was 55 years (range 18–85 years, SD ± 16) and the median follow-up was 653 days per implant [interquartile range (IQR) 337–1058 days]. There were 115 implants placed inside the line of incision. The mean age was 53 years (range 18–83 years, SD ± 15) and the median follow-up was 548 days per implant (IQR 353–1046 days). A number of 81 of 202 patients participated in a clinical trial with a more extensive (standard) follow-up protocol, similarly distributed over the two different cohorts. All the baseline characteristics of the patient population are shown in Table 1. No significant differences in these baseline characteristics between both groups were noticed. The use of longer abutments was equally distributed between the study groups, however, slightly more previous generation implants and abutments were used in the inside group. In Table 2 the other surgical characteristics are summarised. The length of all implants was 4 mm.

Table 1. Background characteristics of the patient population

		Inside		Outside	
		n	*%*	*n*	*%*
Total patients		111	100	92	100
Total implants		115		96	
Gender	Male	43	38.7	38	41.3
	Female	68	61.3	54	58.7
Age at surgery	Mean (years) [±SD]	53 [±15]		55 [±16]	
	Range (years)	18-83		18-85	
Aetiology of hearing loss	Acquired conductive/mixed hearing loss	74	66.7	73	79.3
	Congenital conductive hearing loss	9	8.1	5	5.4
	Single-sided deafness	28	25.2	14	15.2
Comorbidity factors	Mental retardation	5	4.5	3	3.3
	Diabetes mellitus	10	8.9	7	7.6
	Dermatological disease	10	8.9	9	9.8

Table 2. Surgical characteristics of the patient population.

		Inside		Outside	
		n	*%*	*n*	*%*
Total implants		115	100	96	100
Follow-up	Median (days)	548		653	
	Interquartile range (days)	353-1046		337-1058	
Loading time	Mean (weeks) [±SD]	5.5 [±3.2]		5.4 [±3.0]	
Type of implant-abutment	Previous generation Cochlear	14	12.2	5	5.2
	BIA210	9	7.8	3	3.1
	BIA300	36	31.3	35	36.5
	BIA400	0	0	1	1.0
	Ponto Regular	32	27.8	37	38.5
	Ponto Wide	24	20.9	15	15.6
Abutment length	5.5 mm	22	19.1	7	7.3
	6 mm	74	64.3	72	75.0
	8.5 mm	1	0.9	0	0
	9 mm	14	12.2	10	10.4
	10 mm	0	0	1	1.0
	Unknown	4	3.5	6	6.3

Implant loss and revision surgery

Three implants were lost during complete follow-up (1.4 %). All these implants were placed outside the line of incision. One implant was lost 3 days after surgery. The medical chart reported a poor quality of the temporal bone. The other implants were lost after 46 days and after more than 3 years (this patient suffered from recurrent infections with peri-implantitis in the period prior to implant loss).

During the complete follow-up, in 18 of 211 implants, one or multiple revisions were performed (8.5 %). In the group with the implant outside the line of incision, revision surgery was performed in 5 of 96 implants (5.2 %). In the set of implants placed inside the line of incision, revision surgery was undertaken for 13 of 115 implants (11.3 %). This difference in performed revision surgery between both groups, as calculated with a log-rank test, was not significant ($p = 0.129$). An overview of the revision surgery and other therapeutic interventions in both groups is given in Table 3.

Table 3. Overview of therapeutic interventions and revision surgery during follow-up.

[a] Regarding the group with implants placed inside the line of incision: in three implants was two times revision surgery performed, numbers shown indicate how often the procedure is performed.

[b] During this revision procedure was the implant accidently lost while removing the previous abutment, so both a higher abutment and a new implant were placed.

		Inside		Outside	
		n	%	*n*	%
Number of local treatments	0	62	53.9	55	57.3
	1	39	33.9	30	31.3
	2	9	7.8	7	7.3
	3	4	3.5	2	2.1
	4	1	0.9	1	1.0
	5	0	0	0	0
	6	0	0	1	1.0
Number of systemic treatments	0	112	97.4	94	97.9
	1	3	2.6	1	1.0
	2	0	0	1	1.0
Revision surgery[a]	Soft tissue reduction	4		3	
	Secondary higher abutment	7		2	
	New implant	1		0	
	Both soft tissue reduction + higher abutment	3		0	
	Both higher abutment + new implant	1[b]		0	

Soft tissue reaction

The outcome was divided in the presence of a soft tissue reaction (i.e. Holgers grade 1 or higher) and the presence of an adverse soft tissue reaction (i.e. Holgers grade 2 or higher). In 6.7 % of the follow-up contacts a notation of a soft tissue reaction was available but no Holgers classification was given, and in 3.7 % of the follow-up contacts a description about the tissue surrounding the implant was missing. A soft tissue reaction Holgers ≥1 was noticed in 47 implants (49.0 %) when the implant was placed outside the line of incision compared to 70 implants (60.9 %) which were placed inside the line of incision. The median time until the first soft tissue reaction was 90 days (IQR 21–366 days) and 95 days (IQR 44–344 days), respectively.

An adverse soft tissue reaction, Holgers grade ≥2, was registered in 17 implants (17.7 %) when the implant was placed outside the line of incision. In the group of implants placed inside the line of incision, 20 implants (17.4 %) presented with a Holgers ≥2. The median time until the first adverse soft tissue reaction was 363 days (IQR 127–675 days) and 183 days (IQR 112–370 days), respectively.

For both outcome measures a survival curve was calculated by the Kaplan–Meier method; the Kaplan–Meier curves and survival tables are shown in Figures 2 and 3 and Tables 4 and and 5. The Kaplan–Meier curves show the probability of surviving, i.e. not encountering an (adverse) soft tissue reaction, in a given length of time. The corresponding survival tables provide additional information about the cumulative events (CE), remaining cases (RC) and cumulative proportion surviving (CPS) at given points in the time during the follow-up. In these tables, the cumulative events are defined as the number of implants with (adverse) soft tissue reactions and the remaining cases are the implants still in the follow-up without soft tissue problems. The term cumulative proportion surviving can be explained as a statistical representation of the proportion of implants that have not reached the terminal event (i.e. skin reaction) by the end of an interval. A log-rank test was executed to compare the survival curves of the two surgical techniques. No significant differences were found between the two groups for both the presence of soft tissue reactions (p = 0.322) and a Holgers score of 2 or higher (p = 0.951) during the follow-up.

Figure 2. Kaplan-Meier analysis: soft tissue reaction Holgers ≥ 1.

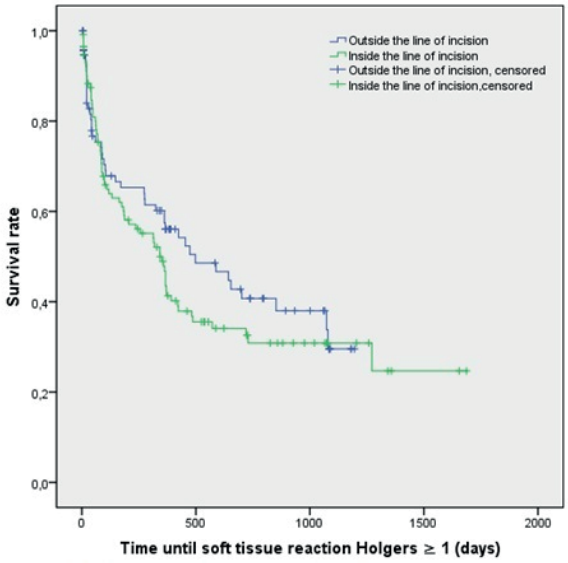


Figure 3. Kaplan-Meier analysis: adverse soft tissue reaction Holgers ≥ 2.

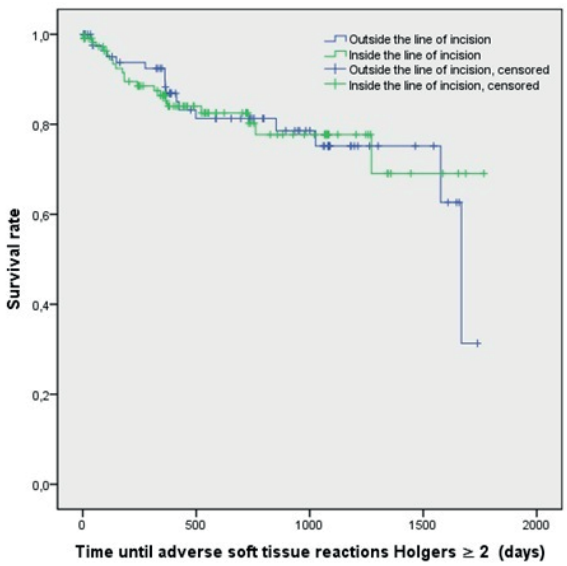


Table 4. Survival table soft tissue reactions Holgers ≥ 1.

CE = Cumulative events, RC = remaining cases, CPS = Cumulative proportion surviving (SE).

	3 months			6 months			12 months			24 months			36 months		
	CE	RC	CPS	CE	RC	CPS	CE	RC	CPS	CE	RC	CPS	CE	RC	CPS
Inside	35	72	0.678 (0.045)	42	63	0.610 (0.047)	56	43	0.468 (0.049)	69	18	0.309 (0.049)	69	7	0.309 (0.049)
Outside	24	57	0.716 (0.049)	29	51	0.653 (0.052)	35	42	0.574 (0.055)	44	20	0.407 (0.061)	47	3	0.296 (0.072)

Table 5. Survival table soft tissue reactions Holgers ≥ 2.

CE = Cumulative events, RC = remaining cases, CPS = Cumulative proportion survival (SE).

	3 months			6 months			12 months			24 months			36 months		
	CE	RC	CPS	CE	RC	CPS	CE	RC	CPS	CE	RC	CPS	CE	RC	CPS
Inside	3	102	0.973 (0.016)	9	94	0.914 (0.027)	14	72	0.864 (0.034)	18	35	0.802 (0.044)	19	14	0.777 (0.050)
Outside	3	76	0.963 (0.021)	5	72	0.937 (0.027)	9	63	0.883 (0.037)	13	39	0.813 (0.048)	15	14	0.752 (0.061)

Discussion

In this historical cohort study, 202 patients and 211 implants were studied with a total median follow-up time of 555 days (IQR 351–1055). No significant differences were found in the presence of postsurgical soft tissue reactions or adverse soft tissue reactions between the two cohorts, i.e. the placement of the percutaneous BAHI inside or outside the line of incision.

As stated in the "Introduction", of all possible techniques for placement of bone-anchored hearing implants the linear incision technique is most popular because of its favourable outcomes.[13,14] Nevertheless, little is known about the placement of the BAHI inside or outside the line of incision, as both techniques are described and used. To our knowledge, this is the first large-scale retrospective study focusing on this particular step in the procedure of implantation with the linear incision technique. Although this retrospective study design and a setting in a tertiary referral centre made it possible to include a relatively large cohort of patients, it might be possible both groups lack patients to detect somewhat smaller differences in the presence of skin reactions.

In addition to the large cohort investigated in this study, other strengths are the representative characteristics of our sample. The rates of implant loss and revision surgery were similar or slightly better compared with previous studies in our centre[7,20] or according to other studies[8,13]. In addition, no differences in baseline characteristics between both groups were noticed.

Despite the fact that the follow-up contacts in the medical charts had few missing data (3.7 %), the retrospective study design could be considered as a limitation of this study. All data were obtained from our Bone Implant database and patients medical charts and during this case analysis, as described in the "Methods", assumptions were made. First of all, in 6.7 % of the follow-up contacts, only a description of the skin surrounding the titanium skin-penetrating implant was documented without a Holgers classification. In these cases, any notation of signs of inflammation was registered as the presence of a soft tissue reaction (i.e. Holgers grade 1 or higher). If there was no notation of inflammation of the skin, it was interpreted as the absence of a soft tissue reaction (i.e. Holgers grade 0). Moreover, it was chosen to exclude

consultation by telephone, because these soft tissue reactions could not be objectified and graded by trained professionals. However, this decision could cause an underestimation of the amount of postoperative skin problems. Furthermore, for some of the background characteristics frequently incomplete patient information was available in the charts.

Another limitation could be confounding caused by the two surgeons performing in principle only one of the surgical techniques for implantation (surgeon A: implant outside the line of incision, surgeon B: implant inside the line of incision). Although the other steps in the surgical procedure were similar, it is inevitable some minor differences in the surgical and peri-operative approaches are present, possibly influencing the outcomes. Ideally, both surgeons should have been performing both the surgical techniques to prevent this confounding factor. This is a limitation of the study design. Moreover, slightly more previous generation implants and abutments were present in the group with implants placed inside the line of incision. This also might have been a confounding factor, because ongoing developments in the field of implants and abutments have led to less skin reactions in the current types.[21]

Finally, the duration of the follow-up of the implants was limited with a median of 653 days (IQR 337–1058 days) and 548 days (IQR 353–1046 days) for implants placed outside and inside the line of incision, respectively. Nevertheless, based on our hypothesis it was expected that differences between both techniques would be seen shortly postoperative, so this relative restricted difference in follow-up was not considered as a serious limitation. In the context of follow-up contacts, it was noticed that 48 patients, slightly unequally divided between the two groups, had less than three follow-up contacts. This can only partially be explained by the group of patients which had received the BAHI most recently. Other reasons might be that patients did not encounter any problems postoperatively, completed their follow-up at another clinic or did not use the BAHA because of (skin) problems. This could influence the outcome positively or negatively.

Future research should be focusing on the sustainability of these already clinically favourable results with new generation implants and abutments. This is also relevant in the context of modifications in the linear incision, for example the linear incision technique with tissue preservation. It has been advocated that this less invasive approach results in faster healing,

better aesthetic appearance and less soft tissue problems. Due to the development of longer abutments, it has been possible to study this proposed modification in the clinical practise. Several recent prospective studies have already shown promising outcomes compared to the traditional technique.[22-26] It has been suggested in the tissue preservation technique to preferably place the implant outside the line of incision. In the light of the outcomes of this evaluation, also in tissue preservation the implant position might not be influencing the outcomes. Additionally, since these implants are also an important hearing rehabilitation option in children, it would be interesting to find out if our results are also valid for this population, especially because implantation in children is more vulnerable to skin problems postoperatively compared to adults.[7,8,11]

In conclusion, no significant difference was found in the presence of soft tissue reactions and adverse soft tissue reaction (i.e. Holgers grade 2 or higher) between the placement of the BAHI inside or outside the line of incision. In the procedure of the linear incision technique used in titanium percutaneous osseointegrated hearing implants for bone conduction hearing, both placing the implant inside and outside the line of incision can be used depending on the surgeons' experience and preferences. In the area of ongoing developments in the surgical procedure, with the goal to further minimise skin problems postoperatively, this study contributes to the knowledge that is available to date.

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4

PERCUTANEOUS BONE-ANCHORED HEARING IMPLANT SURGERY: LINEAR INCISION TECHNIQUE WITH TISSUE PRESERVATION VERSUS LINEAR INCISION TECHNIQUE WITH TISSUE REDUCTION

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Abstract

Objectives: To identify differences in skin thickening and soft tissue reactions between the linear incision technique with tissue reduction (LITT-R) and the linear incision technique with tissue preservation (LITT-P).

Study design: Retrospective cohort study.

Methods: All adult patients who underwent the LITT-R or LITT-P between August 2005 and December 2016 at a large general teaching hospital with a minimum follow-up of 6 months were included.

Results: A total of 83 implants were included using the LITT-R with a median follow-up of 74.0 months. In the LITT-P cohort 58 implants were included with a median follow-up of 16.5 months. Skin thickening was seen in seven implants (8.4%) in LITT-R cohort and 11 implants (19.0%) in the LITT-P cohort in the first 2 years of follow-up (p=0.024). Skin thickening in need of treatment was registered in 5 (6.0%), respectively, 6 (10.3%) implants (p=0.100). Moreover, treatment was successful in all cases. A soft tissue reaction (Holgers≥1) was noticed in 28 (33.7%) implants in the LITT-R group compared to 16 implants (27.6%) in the LITT-P group (p=0.679). An adverse soft tissue reaction (Holgers≥2) was registered in 16 (19.2%), respectively, 2 (3.4%) implants. This difference was significant (p=0.040).

Conclusion: LITT-P has a significantly higher rate of skin thickening and LITT-R has a significantly higher proportion of adverse soft tissue reactions. Nevertheless, combined with the advantages of LITT-P described in other studies, this can be advocated as the preferred technique.

Introduction

In 1977, Tjellström was the first to use a titanium implant in the temporal bone to attach a bone conduction device (BCD), which meant the introduction of the bone-anchored hearing implants (BAHI).[1] Nowadays, the BAHI is an important solution in hearing rehabilitation for patients with uni- and bilateral conductive or mixed hearing loss.[2-4] Moreover, it also improves the quality of life in patients with single-sided deafness.[5]

The first technique used by Tjellström was a two-staged procedure. During the first stage, the implant was placed in the temporal bone and during the second stage, a couple of months later, the skin-penetrating abutment was placed.[1] Later, at least in adults, the surgery was performed as one-staged procedure.[6]. A relevant issue, especially in the first week after placement of the abutment, was the development of soft tissue problems. To prevent these soft tissue problems, Tjellström named two prerequisites.[7] First of all, the skin penetrated by the implant should be hairless to facilitate cleaning of the implant site. Second, the subcutaneous tissue should be removed to minimize skin mobility in relation to the implant. Based on these prerequisites and with the goal to further decrease soft tissue reactions, different surgical techniques were developed over the past decades: the skin graft technique[7,8], the U-shaped flap technique[9], the dermatome technique[9] and the linear incision technique with subcutaneous tissue removal (LITT-R)[10]. The introduction of the aforementioned LITT-R meant several benefits. One of the advantages was the prevention of skin necrosis. Furthermore, it was a fast procedure causing minimal disturbance of the skin.[10] The long-term results show less skin thickening in comparison to the dermatome technique and no differences in soft tissue reactions.[11] Therefore, the LITT-R is advocated as preferred technique.

Next to these developments in surgical techniques, also the field of BAHI has remained dynamic with several interesting improvements in sound processors, abutments and implant design.[12,13] Cochlear® developed the BIA400 with a coating with a hydroxyapatite layer, which is supposed to prevent soft tissue reactions.[12] Oticon Medical®, on the other hand, opted for a smooth surface with the Ponto Wide implant and abutment. Their rationale was that bacteria and biofilm might adhere more strongly to rougher surfaces.[14] Both these recently developed implants could offer more stability[15,16], which led to the possibility to use longer

abutments safely. This was appreciated by both clinicians and patients, because the literature showed a diminishment of most soft tissue reactions after placement of a longer abutment.[17] These developments and findings did encourage the use of the linear incision technique procedure without subcutaneous tissue removal and a longer abutment directly at surgery, i.e. with tissue preservation (LITT-P).

Current research has already shown that the LITT-P is safe, quick and cosmetic favorable.[13,18-23]. In comparison with the dermatome technique, the LITT-P had several benefits: the procedure was faster, the healing time was shorter, there was less sensitivity loss and the cosmetic outcomes were more favorable.[18,24-26] Nevertheless, to our knowledge, there are only three studies comparing the LITT-P to the LITT-R directly. The first study, by Martinez et al.[27], was a relatively small prospective study using the BIA300 (Cochlear) for the LITT-R and the BIA400 (Cochlear) for the LITT-P. The second study, by Van Hoof et al.[28], was a randomized controlled trial and used the same abutments. The third study, by Den Besten et al.[29], was a clinical trial with a historical control-group. In this study, the Ponto Wide (Oticon) was used for both techniques. All three studies showed a significant reduction in the duration of the surgical procedure. Nevertheless, Martinez et al. showed a reduction in early soft tissue reactions, although Den Besten et al. found an increase in soft tissue reactions in the first 6 months (which all recovered completely after topical treatment). Van Hoof et al. found no significant difference in soft tissue reactions, but tissue overgrowth was registered more often in the LITT-R group.

The aim of the current large-scale retrospective study is to determine the difference in skin thickening and soft tissue reactions, the latter classified by the Holgers grading system, between the LITT-R and LITT-P. Interestingly, this study contains both Cochlear and Oticon implanted cases, which enables to perform a subanalysis on these two groups as well.

Materials and Methods

Patients

All patients who received a bone-anchored hearing implant between August 2005 and December 2016 at Deventer Hospital, a large Dutch general teaching hospital, were selected from the local Bone Implant database. Only patients who underwent the LITT-P or LITT-R procedure were included. The minimum follow-up was 6 months. The exclusion criteria were: children (age under 18 years), a two-staged procedure, previous implant removal or loss at the unilateral side and a lack of at least one postoperative follow-up visit at the outpatient clinic.

Post-surgery protocol

The first 39 patients in the LITT-R group received a healing cap and gauze with antibiotic ointment at the end of surgery. All other patients received a healing cap with Mepilex foam (Mölynlycke Health Care, Gothenburg, Sweden). One week after surgery the healing cap was removed during the first postoperative visit and patients received topical therapy with fusidic acid for 2–4 weeks. The subsequent visits were scheduled after 3 weeks, 6 months and 12 months and then every year. In case of any problems, patients or physicians were able to arrange extra visits. During each visit, there was registration of the degree of soft tissue reaction, according to the Holgers' classification and possible skin thickening. Postoperative complications, such as wound dehiscence or implant loss, and possible therapeutic interventions were recorded as well. End of the follow-up was defined as the last follow-up before July 2017.

Case analysis

All medical charts from patients that met the inclusion criteria were reviewed. There was information obtained about the surgical technique, type of implant/abutment/sound processor, post-operative complications, soft tissue reactions, skin thickening, therapeutic interventions, total follow-up time and potential risk factors for soft tissue problems (gender, age, body-mass index, smoking, diabetes mellitus, mental retardation and cardiovascular comorbidities)[31-33].

Soft tissue reactions were graded according to the Holgers classification.[34] A soft tissue reaction was defined as a Holgers 1 or higher and an adverse soft tissue reaction was defined as a Holgers 2 or higher. An adverse soft tissue reaction was an indication for treatment. If the Holgers notation was missing, but there was notation of any redness, swelling, moistness and/or granulation, this was interpreted as the presence of a soft tissue reaction and was graded based on the description and/or treatment. Skin thickening was registered as present or absent. Finally, wound dehiscence was noted as present or absent and implant loss was documented as well.

Statistical analysis

The background characteristics were compared using a Student's t test if there was a normal distribution and a Mann–Whitney U test if there was no normal distribution. To determine if there was a normal distribution, the Kolmogorov–Smirnov test was used. If the outcome was a proportion, the Chi-square test was performed or a Fisher's Exact test if the criteria were not met. The Kaplan–Meier method was used to calculate the survival curves for the presence of skin thickening and soft tissue reactions, A Cox regression for the first 2 years of follow-up was performed to identify any confounding variables and to calculate the (adjusted) Hazard Ratio. For the subgroup analysis the Kaplan–Meier method was used as well with a log-rank test.

The level of significance applied was $p = 0.05$. All our analyses were performed using Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Armonk, NY; IBM Corp), version 24.0.

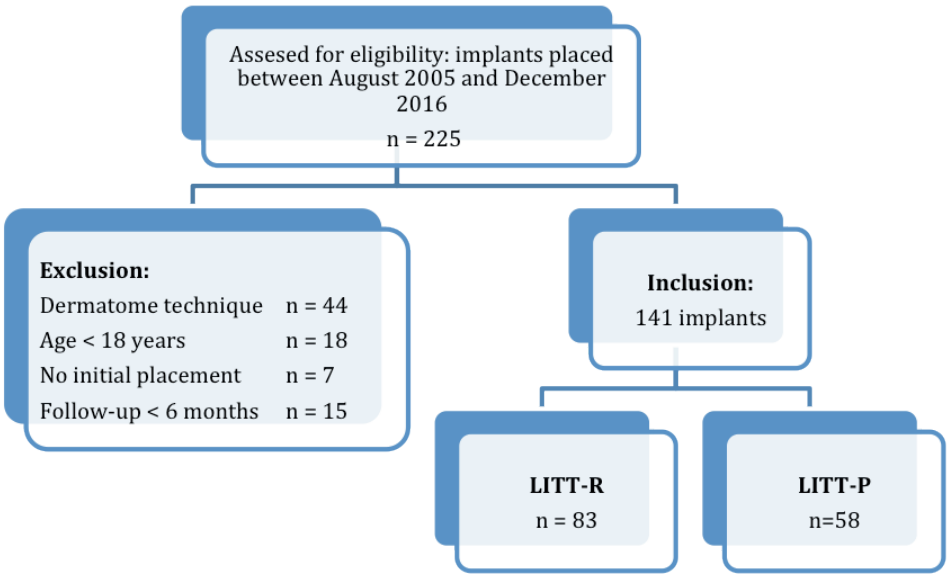
Results

Patients

A total of 225 implants were placed between August 2005 and December 2016. There was exclusion of 84 implants: 44 implants were placed using the dermatome technique, 18 implants were placed in children, seven implants were no initial placement and 15 implants had a follow-up shorter than 6 months. The cohort consisted, therefore, of 141 implants. Five patients received a second, contralateral BAHI over time, so 136 patients were included. All

five bilateral patients received their first BAHI with the LITT-R and their second BAHI with the LITT-P. The flow-chart is found in Figure 1.

Figure 1. Flow-chart inclusion/exclusion



The cohort of the LITT-R consisted of 83 implants with a median follow-up of 74.0 months [interquartile range (IQR) 46.0–106.0]. The LITT-P group contained 58 implants with a median follow-up of 16.5 months (IQR 8.8–28.0). This follow-up is significantly shorter, because the introduction of the LITT-P was in 2013 in this clinic. The background characteristics are summarized in Table 1. The risk factors (age, gender, body mass index, smoking, diabetes mellitus, cardiovascular comorbidity and mental retardation[31-33]) did not differ significantly between the LITT-R and LITT-P cohorts. Finally, an overview of the surgical characteristics is given in Table 2.

Table 1. Summary of the patient characteristics.

	LITT-R		**LITT-P**		***p* values**
	n	%	n	%	
Total implants	83	100	58	100	
Gender					
Male	47	56.6	29	50.0	0.437
Female	36	43.4	29	50.0	
Age at surgery					
Mean (years) [±SD]	59.4 [±13.4]		58.1 [±13.8]		0.459
Range (years)	29- 81		30- 88		
Aetiology of hearing loss					
Conductive/mixed hearing loss	77	92.8	40	69.0	
Single-sided deafness	6	7.2	18	31.0	
Comorbidity factor					
Mean body mass index (kg/m^2) [± SD]	27.3 [±4.4]		27.1 [±4.7]		0.821
Diabetes Mellitus	12	14.5	7	12.1	0.683
Cardiovascular comorbidity	50	60.2	29	50.0	0.228
Mental retardation	5	6.0	2	3.4	0.488
Smoking	19	24.4	12	20.7	0.614

Table 2. Summary of the surgical characteristics.

	LITT-R		**LITT-P**	
	n	%	n	%
Follow-up				
Median (months)	74.0		16.5	
Interquartile range (months)	46.0-106.0		8.8-28.0	
Side				
Right	44	53.0	32	55.2
Left	39	47.0	26	44.8
Implant length				
3 mm Cochlear	4	4.8	1	1.7
4 mm Cochlear	67	80.7	24	41.4
3 mm Oticon	1	1.2	2	3.4
4 mm Oticon	11	13.3	31	53.4

	LITT-R		LITT-P	
	n	%	n	%
Abutment length				
5.5 mm	59	71.1		
6 mm	24	28.9		
8 mm			8	13.8
9 mm			23	39.7
10 mm			11	19.0
12 mm			15	25.9
Implant type				
Previous generation Cochlear	59	71.1		
BIA300	12	14.5		
BIA400			26	44.8
Ponto regular	12	14.5		
Ponto wide			32	55.2
Bottom				
Bone	59	71.1	41	70.7
Dura	18	21.7	10	17.2
Bone/dura	6	7.2	7	12.1

Postoperative complications

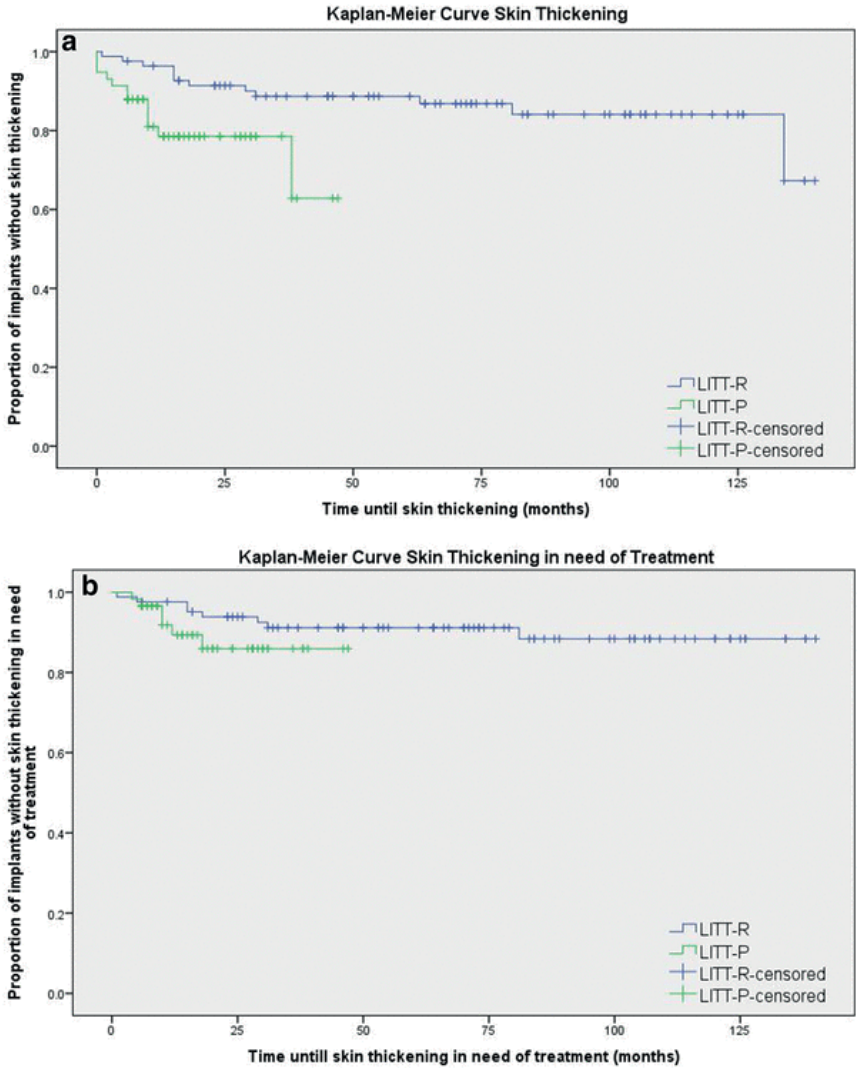
Wound dehiscence was noticed in 28 implants that had been placed with the LITT-R during the complete period of follow-up. Two cases required surgical intervention. One of these patients suffered from a dysregulated coagulation and had persistent blood clots in the wound postoperatively. The other patient was prone to impaired wound healing, because of his risk factors (smoking, overweight, cardiovascular comorbidity). In the other patients, no treatment (n=6) or only topical treatment (n=20) was necessary. After the LITT-P, wound dehiscence was not registered, which was a significant difference ($p<0.001$).

During complete follow-up, four cases of implant loss were seen in the LITT-R cohort. All these cases appeared after at least 6 years of follow-up. One implant was lost after trauma, one probably due to a peri-implantitis and the other two after a period with pain. All four implants were previous generation implants. There was no implant loss in the LITT-P group.

Skin thickening

In the LITT-P cohort, 11 implants (19.0%) had a period of skin thickening after a follow-up of 2 years. In comparison, in the LITT-R group, skin thickening was registered in seven implants (8.4%) in the first 2 years of follow-up. Figure 2a shows the Kaplan Meier curves for skin thickening after both techniques. Using a Cox regression, no confounding variables were found. The hazard ratio for the first 2 years is 3.01 [95% confidence interval (CI) 1.16–7.83, p=0.024]. However, in the LITT-R group five out of the seven implants (71.4%) required therapeutic intervention compared to 6 out of 11 implants (54.5%) in the LITT-P group. Triamcinolone acetide injections were sufficient in all cases that needed treatment in the LITT-P cohort, while in some cases of the LITT-R cohort an abutment change or soft tissue reduction was needed. Figure 2b shows the Kaplan–Meier curves of skin thickening in need of treatment, i.e. significant skin thickening. Gender was found to be a confounding variable. Adjusted for gender, the hazard ratio found with a Cox regression for the first 2 years is 2.77 (95% confidence interval 0.82–9.33, p=0.100). The therapeutic interventions were eventually successful in all cases.

Figure 2. A. Kaplan-Meier curve skin thickening. B. Kaplan-Meier curve skin thickening in need of treatment.

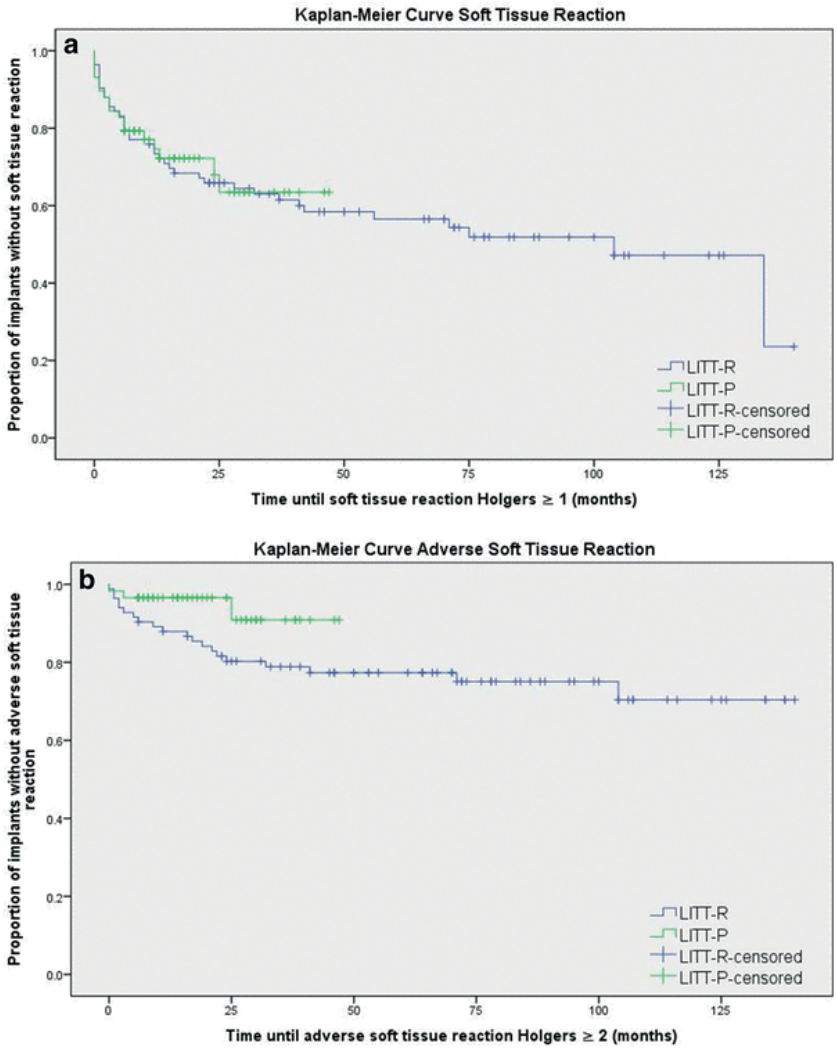


Soft tissue reactions

The development of a soft tissue reaction, i.e. Holgers grade 1 or higher, was registered in 16 implants (27.6%) in the LITT-P cohort within the first 2 years of follow-up. In comparison, 28 (33.7%) implants had a soft tissue reaction after the LITT-R procedure within this period of time. An adverse soft tissue reaction (≥Holgers 2) was seen in two patients (3.4%) of the LITT-P group and in 16 implants (19.2%) of the LITT-R group within the first 2 years. The

Kaplan–Meier curves can be found in Figure 3. The Cox regression showed gender, smoking, BMI and cardiovascular risk factors as confounding variables for soft tissue reactions. The adjusted hazard ratio for the first 2 years is 0.876 (95% CI 0.47–1.64, p=0.679). There were no confounding variables for adverse soft tissue reactions; the hazard ratio is 0.213 (95% CI 0.05–0.931, p=0.040).

Figure 3. A. Kaplan-Meier curve soft tissue reaction. B. Kaplan-Meier curve adverse soft tissue reaction



A summary of the main outcomes can be found in Table 3.

Table 3. Summary of main outcomes. * Level of significance $p = 0.05$.

	LITT-R		**LITT-P**		***p* values**	**HRR**
	n	%	n	%		
Total implants	83	100	58	100		
Postoperative complications						
Implant loss	4	4.8	0	0		
Wound dehiscence	28	33.7	0	0	<0.001*	
Skin thickening						
First 2 years	7	8.4	11	19.0	0.024*	3.01
Total Follow-up	12	14.5	12	20.7		
Skin thickening in need of treatment						
First 2 years	5	6.0	6	10.3	0.100	2.77
Total Follow-up	8	9.6	6	10.3		
Soft tissue reaction						
First 2 years	28	33.7	16	27.6	0.679	0.876
Total Follow-up	38	45.8	17	29.3		
Adverse soft tissue reaction						
First 2 years	16	19.2	2	3.4	0.040*	0.21
Total Follow-up	20	24.1	3	5.2		

Previous generation implant (flange fixture)

As mentioned, a relevant difference between the LITT-R and LITT-P cohort is the implantation of previous generation implants, because these were only used in the LITT-R group. In this cohort, all implants placed before 2009 were previous generation implants. In 14 out of 59 of these implants, adverse soft tissue reactions were seen after 3 months of follow-up. If the newer implants in this group, i.e. the BIA300 and Ponto regular (n=24), are considered exclusively, it is worth mentioning that no adverse soft tissue reactions occurred after 3 months of follow-up. In this context, a Kaplan–Meier analysis with log-rank test was performed between the LITT-P cohort and the LITT-R cohort without previous generation implants for the first 2 years. The results are shown in Table 4.

Table 4. Overview of the outcomes between LITT-P and LITT-R without previous generation implant (for the first 2 years). * Level of significance $p = 0.05$.

	LITT-R without previous generation		**LITT-P**		***p* values**
	n	%	n	%	
Total implants	24		58		
Skin thickening	1	4.2	11	19.0	0.055
Skin thickening in need of treatment	1	4.2	6	10.3	0.213
Soft tissue reaction	5	20.8	16	27.6	0.411
Adverse soft tissue reaction	2	8.3	2	3.4	0.394

BIA400 vs. Ponto Wide

Within the group of the LITT-P, two types of implants were used: the BIA400 and the Ponto Wide. In the BIA400 group, skin thickening was recorded in nine out of 26 implants (34.6%). In comparison, in the Ponto Wide group, it was recorded in three out of 29 implants (9.4%). This difference was significant (p=0.026) as calculated with a Kaplan–Meier analysis with log-rank test. Skin thickening in need of treatment occurred in four BIA400 implants and two Ponto Wide implants, which was not significantly different (p=0.270).

A soft tissue reaction Holgers≥1 was registered in ten out of 26 BIA400 implants (38.5%) compared to seven out of 32 Ponto Wide implants (21.9%). The Kaplan–Meier analysis with log-rank test showed that this was not significantly different (p=0.219). Adverse soft tissue reactions, i.e. Holgers≥2, only occurred two times in the Ponto Wide group and one time in the BIA400 group (p=0.517).

Discussion

In this historical cohort study, a total of 141 implants were included: 83 implants were placed using the linear incision technique with tissue reduction (LITT-R) with a median follow-up of 74.0 months and 58 implants were placed using the linear incision technique with tissue preservation (LITT-P) with a significantly shorter median follow-up of 16.5 months. There was significantly more skin thickening in the LITT-P cohort compared to the LITT-R group during the first 2 years. Nevertheless, adverse soft tissue reactions and wound dehiscence occurred

significantly more often in the LITT-R group. The rate of implant loss was 4.8% in LITT-R after a median follow-up of 74.0 months. In LITT-P there has not been any loss after a median follow-up of 16.5 months.

Last decades, there have been a lot of improvements and modifications in BAHI. An important development was the introduction of wider diameter implants. These implants could provide more stability and, therefore, longer abutments could be used. This resulted in the possibility to perform surgery without subcutaneous tissue removal: the LITT-P. Recent studies have been showing a lot of advantages of tissue preservation compared to tissue reduction during surgery. It is faster and easier to perform, it is cosmetically favourable and there is less numbness, a shorter healing time and good patient satisfaction.[13,18,20-27,29]

However, there is only little known about soft tissue reactions and skin thickening in patients undergoing the LITT-P procedure after the first year of follow-up in comparison to the LITT-R technique. To our knowledge, only three studies compared the LITT-P to the LITT-R[27-29], with more or less contradicting results. Moreover, none of these studies had a follow-up of more than 1 year. The current study has a median follow-up of 16.5 months for the LITT-P cohort and a median of 74.0 months for the LITT-R cohort. Furthermore, with 58 implants in the LITT-P cohort, it is also the largest one. The aforementioned makes this study valuable in the dynamic field of BAHI-surgery.

Skin thickening

In the current study, skin thickening occurred significantly more often in the LITT-P group. A possible explanation for this result can be friction between the abutment and subcutaneous tissue. This friction may cause skin thickening as a reaction. After the surgical technique with tissue preservation, there is a larger surface of tissue in contact with the abutment, which can cause more mechanical forces on the tissue. Nevertheless, skin thickening resolved in all cases, so this was a minor drawback only.

Soft tissue reactions

Adverse soft tissue reactions, on the other hand, occurred significantly more in the LITT-R cohort. In this cohort the flange fixture implant, the BIA300 and the Ponto Regular implant were used. Some patients with the flange fixture implant experienced the onset of adverse

soft tissue reactions after 3 months of follow-up. These 'late' adverse soft tissue reactions were not seen in any of the other implants. Hultcrantz et al.[15] also described that the flange fixture implant had significantly more long term soft tissue reactions than the BIA300. Therefore, we also compared the LITT-R without the flange fixture implants to the LITT-P. This subanalysis showed no longer a significant difference in adverse soft tissue reactions. The hypothesis could be that interruption of the skin is the main contributing factor to soft tissue reactions, which cannot be completely resolved by further improving the percutaneous surgical technique. To prevent soft tissue reactions, transcutaneous techniques may offer opportunities. However, these transcutaneous devices have several challenges and concerns in the context of audiological output, MRI compatibility and pressure-related skin problems.[35]

BIA400 vs. Ponto Wide

The BIA400 and the Ponto Wide implants have been used for the LITT-P procedure. To our knowledge, there are no previous studies comparing these two implants. In this study, there was no significant difference in soft tissue reactions between the BIA400 and Ponto Wide, but skin thickening was noticed significantly more (p=0.026) in the cohort of the BIA400. A possible explanation for this might be the shape of the abutments (see Figure 4). The diameter of the Ponto Wide increases outside the skin whilst the increase in diameter of the BIA400 is positioned in the subcutaneous part of the abutment. This might cause more friction. Another difference is the hydroxyapatite coating versus a smooth titanium surface. With a total of 26 BIA400 implants and 29 Ponto Wide implants, the size of both groups is decent. However, not large enough for powerful statistical analysis and, therefore, larger population and longer follow-up is necessary before final conclusions can be drawn. Currently, patients choose the brand of the implant based on preferences for a specific sound processor.

Figure 4. BIA400 'Copyright Cochlear Limited' (left), Ponto Wide 'Copyrigth Oticon Medical' (right).

Strengths and limitations

As mentioned above, the size of the cohorts and the length of follow-up are two important strengths of this study. Furthermore, regarding the subjective interpretation of most of the outcome measures, it is an asset of this study that both surgical techniques were performed by the same surgeon as well as follow-up was mainly done by the same surgeon. Moreover, differences in other aspects of the surgical and perioperative approaches could be minimized to prevent possible confounding bias. Finally, the background characteristics of both groups were comparable and the rates of soft tissue reactions, skin thickening and implant loss were comparable to other studies.[10,19-21,23,24,29,36-40]

A limitation of the retrospective study design is a lower accuracy of the data collection. Since the patients themselves were responsible for making yearly appointments, there was loss of patients to follow-up over the years. The division of these cohorts by time, i.e. the LITT-P replaced the LITT-R and, therefore, the two techniques were not used simultaneously, should be considered. This resulted both in a shorter follow-up time for the LITT-P group and the fact that the surgeon was already experienced in BAHI surgery in general when he started using the LITT-P.

As mentioned, five different kinds of implants were used in this study. This is a limitation of this study, but may also be considered as a strength. Although it might seem like adding a

confounding variable, it is a fact that different implants are used for the LITT-P and LITT-R anyway. The value of using both brands is the possibility to make some comparisons.

What is next?

Recently, the so-called punch technique was introduced. In this procedure, no linear incision is made (only a punch hole). In the current literature, there are no studies comparing the punch technique to the LITT-P, but a study protocol for a randomized controlled trial had been submitted.[41] The advantages of this technique are shorter surgical time and minimization of scar tissue.[42,43] However, in our experience, the scar with the LITT-P is already very minimal and well healing. The disadvantage of the punch technique is that bleeding during surgery is harder to control[42] and there are several studies that experienced more implant loss[44,45].

Conclusion

In conclusion, this well-designed, large-scale historical cohort study showed that skin thickening is significantly more encountered after the LITT-P. All cases could be treated successfully. Adverse soft tissue reactions were seen significantly more in the LITT-R cohort. Another advantage of the LITT-P is the absence of wound dehiscence. In combination with the already known favourable results of the LITT-P, such as less numbness, a shorter procedure and cosmetically favourable outcomes, this seems to outweigh the disadvantage of skin thickening. The LITT-P should be advocated as preferred technique.

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5

LONG-TERM OUTCOMES OF THE MINIMALLY INVASIVE PONTO SURGERY VS. LINEAR INCISION TECHNIQUE WITH SOFT TISSUE PRESERVATION FOR INSTALLATION OF PERCUTANEOUS BONE CONDUCTION DEVICES

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Abstract

Objective: Comparing the surgical outcomes of the Minimally Invasive Ponto Surgery (MIPS) technique with the linear incision technique with soft tissue preservation (LITT-P) for bone conduction devices after a follow-up of 22 months.

Methods: In this multicenter randomized controlled trial, there was the inclusion of 64 adult patients eligible for unilateral surgery. There was 1:1 randomization to the MIPS (test) or the LITT-P (control) group. The primary outcome was an (adverse) soft tissue reaction. Secondary outcomes were pain, loss of sensibility, soft tissue height/overgrowth, skin sagging, implant loss, Implant Stability Quotient measurements, cosmetic scores, and quality of life questionnaires.

Results: Sixty-three subjects were analyzed in the intention-to-treat population. No differences were found in the presence of (adverse) soft tissue reactions during complete follow-up. Also, there were no differences in pain, wound dehiscence, skin level, soft tissue overgrowth, and overall quality of life. Loss of sensibility (until 3-month post-surgery), cosmetic scores, and skin sagging outcomes were better in the MIPS group. The Implant Stability Quotient was higher after the LITT-P for different abutment lengths at various points of follow-up. Implant extrusion was nonsignificantly higher after the MIPS (15.2%) compared with LITT-P (3.3%).

Conclusion: The long-term results show favorable outcomes for both techniques. The MIPS is a promising technique with some benefits over the LITT-P. Concerns regarding nonsignificantly higher implant loss may be overcome with future developments and research.

Introduction

Bone conduction devices (BCDs) have become increasingly important in hearing rehabilitation. The BCD comprises a retro-auricular implant in the skull to which a sound processor is connected via a skin-penetrating abutment.[1] Treatment with a BCD is indicated in patients with uni- and bilateral conductive or mixed hearing loss, with intolerance or inability to wear conventional hearing aids[1-3], or in patients with single-sided deafness[4]. BCD surgery is considered a safe procedure with a low risk of complications.[5] Soft tissue problems, including peri-abutment inflammation (as graded by the Holgers Index[6]), skin thickening, and tissue overgrowth, do occur. Other complications are numbness and pain at the implant site, pain, postoperative wound dehiscence or skin necrosis, and implant extrusion.[5,7] Therefore, further development of implantation techniques and improvements of the BCD implants would be beneficial.

Besides variations in implant and abutment design, for example, the hydroxyapatite layer of the BIA400 from Cochlear (Mölnlycke, Sweden)[8,9] and the smooth titanium surface of the Ponto Wide from Oticon Medical AB (Askim, Sweden)[10,11], there have been advances in surgical techniques. Initially, subcutaneous tissue was removed in an attempt to reduce friction skin movements around the abutment. Different surgical techniques were introduced, including the free retro-auricular full-thickness skin graft, pedicled grafts, the dermatome technique, and finally leading up to the universally adopted linear incision technique with tissue reduction (LITT-R).[12,13] Of these surgical techniques, the LITT-R gained popularity because it leads to fewer complications and is a straightforward procedure.[13-15] A different approach to achieve reduced soft tissue reaction is the usage of transcutaneous BCDs. These are abutment-free, which might reduce soft tissue problems.[16] However, audiological outcomes are often less favorable due to attenuation of (sound) vibration by the soft tissue.[17,18] For the percutaneous devices, in the context of surgical techniques, the linear incision technique with soft tissue preservation (LITT-P) was developed based on this principle of less invasive surgery. Studies did show improved outcomes, including more favorable cosmetic results, less numbness, and shorter surgical time.[19-25] The vast majority of the previous studies evaluating the outcome of this technique suggested similar or less (adverse) soft tissue reactions in comparison with the LITT-R.[7,24-28]

Recently, to further reduce soft tissue reactions, the surgical procedure was simplified to a minimally invasive, so-called punch-only technique.[29-32] These procedures with a punch-hole only should theoretically result in less soft tissue trauma. Over the last years, several surgeons performed this principle of punch-only technique and described improved cosmetic results and shorter surgical procedure time without observing more soft tissue problems in comparison with the dermatome or linear incision technique.[29-32] A standardized approach for the technique was lacking. This was the reason for Oticon Medical AB (Askim, Sweden) to introduce a new standardized punch-only technique, including a surgical kit: the Minimally Invasive Ponto Surgery (MIPS)[33].

The short-term results of a multicenter evaluation using the MIPS were encouraging with minimal intraoperative complications (e.g., only one case of a cerebrospinal fluid leak in 77 implants). Also, the outcomes regarding soft tissue reactions (5.0% adverse soft tissue reactions recorded in 160 visits) and implant survival rates (96.1% at 20 weeks) were promising.[33] Moreover, another direct cost comparison study demonstrated a reduction in cost with the MIPS in comparison with the linear incision approach.[34] In a multicenter randomized controlled trial, Calon et al.[35] compared the MIPS technique with the LITT-P. After 3 months of follow-up, the MIPS resulted in significantly less skin sagging and numbness of the skin. Furthermore, there was a significant reduction of surgical time and an improvement in cosmetic outcomes. There were no significant differences in soft tissue inflammation (Holgers score ≥ 2) between the procedures. Nonetheless, a nonsignificant increase in implant extrusion rate was found when using the MIPS technique.[35] Besides these encouraging short-term results, however, there is only one small prospective cohort study of Sardiwalla et al.[36] with a longer follow-up (minimal 12 months). This study concluded device stability and patient satisfaction with the MIPS procedure.[36]

These findings warrant exploration of the long-term results of the MIPS technique. The current study will compare the surgical outcomes of the MIPS procedure with the LITT-P after a follow-up of 22 months. To our knowledge, this is the first well-designed, multicenter randomized controlled study that will present and discuss the long-term results of the MIPS technique.

Materials and Methods

Study Design and Subjects

This study is a multicenter randomized controlled trial in the Netherlands (Maastricht University Medical Centre, Ziekenhuisgroep Twente, and Medisch Centrum Leeuwarden). The protocol of this study was published previously[37], as well as the surgical outcomes after 3 months of follow-up[35].

The inclusion criteria were eligibility for unilateral BCD surgery[38] in combination with an adult age (≥18 years). Patients with a history of immunosuppressive disease and/or systemic immunosuppressive medication, relevant dermatological disease, bilateral BCD placement, and participation in other studies were excluded. In case of the preoperative absence of a suitable implantation site for a 4.0-mm implant or insufficient bone quality, the subject was regarded as early termination and excluded from the study. All enrolled subjects were randomized in each research center independently in a 1:1 ratio stratified for sex. The test group was the MIPS technique, and the control cohort was the LITT-P.

Surgical Technique and Post-surgery Protocol

All otorhinolaryngologists were experienced in the LITT-P procedure and had instruction and training in the MIPS procedure. Depending on patient preferences, local or general anesthesia was administered. Measurement of the skin thickness (before application of local anesthesia) was used to determine the abutment length. In both techniques, a Ponto-wide 4-mm implant with a premounted abutment (9, 12, or 14 mm) was installed using an insertion torque setting of 40–50 Ncm (Oticon Medical, Askim, Sweden).

The procedure of the LITT-P (control group) consists of a longitudinal incision, which is located to the ear canal posterosuperior. The implant is placed in the temporal bone after mobilizing the skin and subcutaneous tissue and exposure of the periosteum. The skin is punched outside the incision line, and the abutment is guided through the punch hole. For the MIPS technique (test group), an incision was created with a 5-mm punch with the removal of the remaining soft tissue and periosteum in the punch hole. The implant positioning is similar to the LITT-P. A cannula is inserted at the surgical site, and, after that, the hole is created with the cannula guide drill followed by the cannula widening drill. Then, the implant

with abutment is installed, assisted with the insertion indicator. There is an extensive deliberation of both surgical techniques, including step-by-step illustrations in the study protocol[37].

The assessment of the patients was at baseline, surgery, 9 days postoperative, 3 weeks post-surgery, and after 3, 12, and 22 months of follow-up. Patients or physicians could initiate extra visits in case of complications, other problems, or individual requests. The different outcome measures were registered accurately during all these follow-up appointments at different points in time.

Outcome Measures

The primary outcome is the incidence of an adverse soft tissue reaction (Holgers index ≥ 2) between surgery and 22 months of follow-up. Secondary outcomes are pain directly around the abutment or related to the implant, loss of sensibility of the skin, wound dehiscence, soft tissue height/overgrowth, presence of skin sagging, implant loss, and implant stability quotient (ISQ) measurements. The cosmetic result score (graded using a 10-point scale) is measured after 3-, 12-, and 22-months follow-up. The tertiary outcomes consist of quality of life questionnaires: the Health Utilities Index Mark III (HUI-III), Abbreviated Profile of Hearing Aid Benefit (APHAB), and ICEpop CAPability measure for Adults (ICECAP-A). These questionnaires were executed at baseline consultation and after 12 and 22 months or any visit with an adverse soft tissue reaction. Also, complications, adverse events, and serious adverse events were recorded.

Statistical Analysis

The data analysis was conducted by Statistika Konsultgruppen (Gothenburg, Sweden). An intention-to-treat (ITT) and per-protocol (PP) population analysis was performed for all surgical outcomes. The level of statistical significance applied was $p = 0.05$.

The statistical test for the primary outcome adverse soft tissue reactions was a chi-square test and Fisher's exact test. Additionally, a Mantel–Haenszel chi-square test was executed to identify differences in Holgers scores. For the secondary and tertiary outcomes, the comparison between the cohorts in the presence of sensibility loss, skin sagging, wound dehiscence, and soft tissue overgrowth (i.e., the number of abutment replacements and

revision surgeries) was performed with a Fisher's exact test. The analysis of the endpoints pain, area of sensibility loss, skin level, ISQ measures (high and low), cosmetic results, and all quality of life questionnaires was with a Mann–Whitney U-test. A Kaplan–Meier curve was created for the implant extrusion, and a log-rank test was executed to compare both groups.

Ethics

This study was performed in accordance with ISO 14155:2011 and the Declaration of Helsinki. There was approval by the ethics committee at Maastricht University Medical Centre+ (NL500720.068.14), Medisch Centrum Leeuwarden, and Ziekenhuisgroep Twente. Also, there was registration in ClinicalTrials.gov NCT02438618. The participation of subjects was voluntary, and all subjects provided written informed consent. The study is sponsored by Oticon Medical AB (Askim, Sweden). The investigators had full access to all data. Monitoring was performed independently.

Results

Baseline Characteristics

Sixty-four participants were included between December 2014 and August 2016. Thirty-three subjects were randomized to the test cohort (52%) and 31 to the control cohort (48%). There was the exclusion of one patient during surgery because of the placement of a 3-mm implant. This resulted in 63 subjects being analyzed in the ITT analysis. Due to implant loss and protocol deviations (mainly visits out of the window but also missed standard visits), 25 subjects were excluded from the ITT group, which resulted in a total PP population of 38 participants (Figure 1). Baseline characteristics were comparable between the groups (for both ITT and PP population, see Table 1, Supplementary Table 1).

Figure 1. Subject flow chart.

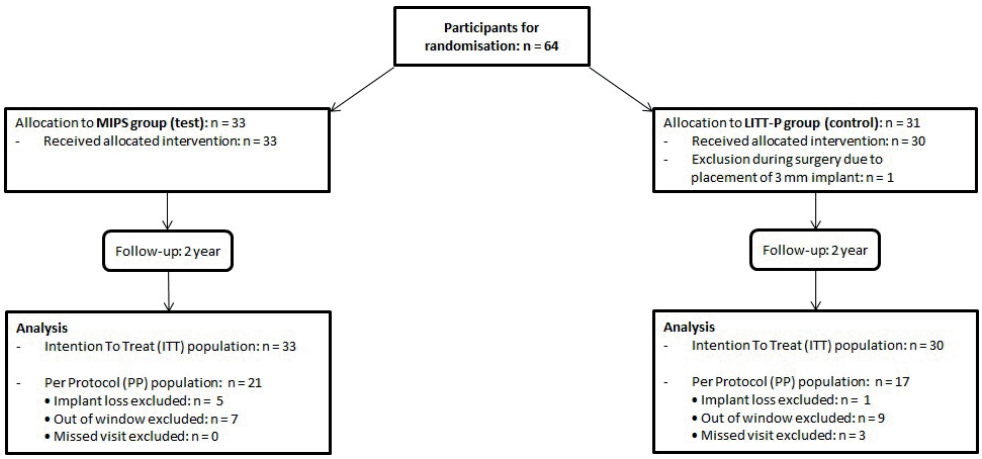


Table 1. Baseline characteristics intention-to-treat population.

Baseline characteristics	MIPS (n = 33)	LITT-P (n = 30)	*p*-value
Age (years)			
Mean (SD), 95 %- CI	50.3 (16.3), 44.5; 56.1	51.9 (16.1), 45.9; 57.9	0.52
Median (Min- Max)	51.0 (19.0- 80.0)	58.5 (21.0- 75.0)	
Gender			
Male	12 (36.4 %)	11 (36.7 %)	1.00
Female	21 (63.6 %)	19 (63.3 %)	
Type of hearing losse			
Acquired conductive/mixed hearing loss	26 (78.8 %)	25 (83.3 %)	
Single sided deafness	6 (18.2 %	5 (16.7 %)	0.62
Congenital conductive hearing loss	1 (3.0 %)	0 (0.0 %)	
Smoking			
Yes	7 (21.2 %)	8 (26.7 %)	0.83
No	26 (78.8 %)	22 (73.3 %)	
Body Mass Index (BMI; kg/m2)			
Mean (SD), 95 %- CI	27.4 (6.4), 25.2; 29.7	28.4 (5.7), 26.2; 30.5	0.36
Median (Min- Max)	27.2 (19.6- 44.4)	26.7 (20.6- 45.0)	

Ethinicity			
Caucasian	33 (100.0 %)	30 (100.0 %)	
Implantation site			
Right	17 (51.5 %)	13 (43.3 %)	0.69
Left	16 (48.5 %)	17 (56.7 %)	
Abutment length			
9	21 (63.6 %)	13 (43.3 %)	0.11
12	10 (30.3 %)	16 (53.3 %)	0.064
14	2 (6.1 %)	1 (3.3 %)	

Primary Outcome

There was no difference in adverse soft tissue reaction (Holgers ≥ 2) during the 22-month follow-up between the MIPS and LITT-P groups in either the ITT or the PP populations (Table 2, Supplementary Table 2, Figure 2, Supplementary Figure 1). Sensitivity analyses did not reveal any significant difference either. Moreover, no difference was found in the maximum Holgers index between the groups.

Figure 2. Stacked bar chart for the highest observed Holgers Index scores during standard follow-up visits. In the right-sided figure (B), missing data were corrected with the last observation carried forward technique. The last visit ('2 years') was at 22 months of follow-up.

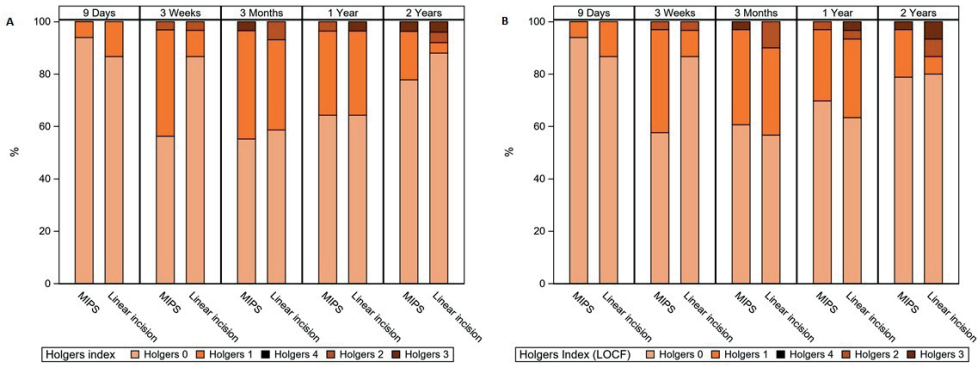


Table 2. Primary and secondary outcomes (ITT population). Continuous variables are presented as mean (SD, 95% CI) and median (min- max) with n. A significant p-value ($p < 0.05$) is showed in bold.

Pain is graded in a 10-point scale with a scale of 0 representing absence of pain to 10 representing the worst pain. In cases of missing values, there was calculated a correction with the last observation carried forward (LOCF) technique, which did either not show significant differences. The area of sensibility loss is registered as the most outward diameter from abutment (in mm). The cosmetic observed variables are rated as 1 being no difference with the healthy contralateral site and with 10 being the most negative difference with the healthy situation. In contrast, the overall cosmetic score and patient satisfaction will be rated with 10 being the best cosmetic result. The skin level is measured as the distance between the top of the abutment to the skin in four quadrants (in mm).

	MIPS (n = 33)	**LITT-P (n = 30)**	***p*-value**
Primary outcome: (adverse) soft tissue reactions			
Adverse soft tissue reaction (Holgers ≥ 2) from surgery to 22 months	8 (24.2 %)	11 (36.7 %)	0.28
Adverse soft tissue reaction (Holgers ≥ 2) from surgery to 22 months (with the Fisher's Exact Test)	8 (24.2 %)	11 (36.7 %)	0.42
Adverse soft tissue reaction (Holgers ≥ 2) from surgery to 22 months (Sensitivity analysis: highest observed Holgers score plus one)	8 (24.2 %)	11 (36.7 %)	0.28
Adverse soft tissue reaction (Holgers ≥ 2) from surgery to 22 months (Sensitivity analysis: all observed implant losses have experienced a Holgers Index score of four)	12 (36.4 %)	11 (36.7 %)	0.98
Maximum Holgers Index at standard and extra visits			
0 No irritation	11 (33.3 %)	6 (20.0 %)	
1 Slight redness	14 (42.4 %)	13 (43.3 %)	
2 Red and slightly moist tissue	4 (12.1 %)	9 (30.0 %)	
3 Reddish and moist tissue, sometimes granulation formation	4 (12.1 %)	2 (6.7 %)	0.38
4 Profound signs of infection resulting in implant removal	0 (0.0 %)	0 (0.0 %)	

	MIPS (n = 33)	LITT-P (n = 30)	*p*-value
Secondary outcome: pain			
Pain around the implant			
9 days	1.39 (1.87, 0.73;2.06) 0.00 (0.00- 6.00) n = 33	1.97 (2.61, 0.99;2.94) 1.00 (0.00- 8.00) n = 30	0.50
3 weeks	0.938 (1.216, 0.499;1.376) 0.00 (0.00- 4.00) n = 32	1.000 (1.619, 0.396;1.604) 0.00 (0.00- 6.00) n= 30	0.67
3 months	1.38 (2.23, 0.53;2.23) 0.00 (0,00- 8.00) n = 29	1.17 (2.04, 0.40;1.95) 0.00 (0.00- 7.00) n = 29	0.54
12 months	0.778 (1.739, 0.090;1.466) 0.00 (0.00- 6.00) n = 27	1.54 (2.43, 0.59;2.48) 0.00 (0.00- 8.00) n= 28	0.23
22 months	0.889 (2.190, 0.023;1.755) 0.00 (0.00- 9.00) n = 27	0.680 (1.492, 0.064;1.296) 0.00 (0.00- 5.00) n = 25	0.97
Radiating pain from the implant			
9 days	0.606 (1.657, 0.018;1.194) 0.00 (0.00- 7.00) n = 33	0.500 (1.570,-0.086;1.086) 0.00 (0.00- 8.00) n = 30	0.95
3 weeks	0.563 (1.390, 0.061;1.064) 0.00 (0.00- 5.00) n = 32	0.433 (1.357,-0.073;0.940) 0.00 (0.00- 5.00) n = 30	0.39
3 months	0.759 (1.864, 0.050;1.468) 0.00 (0.00- 6.00) n = 29	0.759 (1.883, 0.042;1.475) 0.00 (0.00- 7.00) n = 29	0.77
12 months	0.571 (1.814,-0.132;1.275) 0.00 (0.00- 8.00) n = 28	0.464 (1.453,-0.099;1.028) 0.00 (0.00; 6.00) n = 28	0.75
22 months	0.481 (1.868,-0.258;1.221) 0.00 (0.00- 9.00) n = 27	0.200 (0.707,-0.092;0.492) 0.00 (0.00- 3.00) n = 25	1.00
Headache related to the BCD			
9 days	0.424 (1.393,-0.070;0.918) 0.00 (0.00- 7.00) n = 33	1.30 (2.39, 0.41;2.19) 0.00 (0.00- 8.00) n = 30	0.077

		MIPS (n = 33)	LITT-P (n = 30)	*p*-value
3 weeks		0.375 (1.476,-0.157;0.907) 0.00 (0.00- 6.00) n = 32	0.300 (1.317,-0.192;0.792) 0.00 (0.00- 7.00) n = 30	0.96
3 months		0.793 (2.094,-0.003;1.590) 0.00 (0.00- 8.00) n = 29	0.241 (0.830,-0.075;0557) 0.00 (0.00- 4.00) n = 29	0.59
12 months		0.464 (1.478,-0.109;1.037) 0.00 (0.00- 6.00) n = 28	0.00 (0.00, 0.00;0.00) 0.00 (0.00- 0.00) n = 28	0.081
22 months		0.296 (1.540,-0.313;0.905) 0.00 (0.00- 8.00) n = 27	0.280 (1.400,-0.298;0.858) 0.00 (0.00- 7.00) n = 25	1.00
Secondary outcome: sensibility				
Area loss of sensibility				
9 days		2.70 (6.13, 0.52;4.87) 0.00 (0.00- 25.00) n = 33	13.5 (21.0, 5.6;21.3) 4.5 (0.00- 100.0) n = 30	**0.005**
3 weeks		0.375 (1.040, 0.000;0.750) 0.00 (0.00- 5.00) n =32	8.23 (17.25, 1.79;14.68) 0.00 (0.00- 70.00) n = 30	**0.013**
3 months		0.138 (0.516,-0.058;0.334) 0.00 (0.00;2.00) n =29	5.79 (13.75, 0.56;11.02) 0.00 (0.00- 60.00) n = 29	**0.0076**
12 months		0.679 (2.374,-0.242;1.599) 0.00 (0.00- 10.00) n = 28	2.93 (10.18,-1.10;6.95) 0.00 (0.00- 50.00) n = 27	0.60
22 months		1.000 (4.472,-1.093;3.093) 0.00 (0.00- 20.00) n = 20	0.222 (0.943,- 0.247;0.691) 0.00 (0.00- 4,00) n = 18	1.00
Presence of loss of sensibility?				
9 days	No	24 (72.7 %)	13 (43.3 %)	**0.034**
	Yes	9 (27.3 %)	17 (56.7 %)	
3 weeks	No	27 (84.4 %)	18 (60.0 %)	0.061
	Yes	5 (15.6 %)	12 (40.0 %)	
3 months	No	27 (93.1 %)	19 (65.5 %)	**0.021**
	Yes	2 (6.9 %)	10 (34.5 %)	
12 months	No	25 (89.3 %)	23 (85.2 %)	0.96
	Yes	3 (10.7 %)	4 (14.8 %)	
22 months	No	19 (95.0 %)	17 (94.4 %)	1.00
	Yes	1 (5.0 %)	1 (5.6 %)	

	MIPS (n = 33)	LITT-P (n = 30)	*p*-value
Secondary outcome: cosmetic appearance			
Natural skin position			
3 months	2.72 (1.10, 2.31;3.14) 3.00 (1.00- 5.00) n = 29	3.48 (1.38, 2.96;4.01) 3.00 (1.00- 6.00) n = 29	**0.025**
12 months	2.07 (1.15, 1.62;2.52) 2.00 (1.00- 5.00) n = 28	2.82 (1.33, 2.30;3.34) 3.00 (1.00- 5.00) n = 28	**0.026**
22 months	2.12 (1.72, 1.41;2.83) 2.00 (1.00- 8.00) n = 25	2.23 (1.54, 1.54;2.91) 2.00 (1.00- 7.00) n = 22	0.46
Extent of baldness			
3 months	2.24 (0.79, 1.94;2.54) 2.00 (1.00- 4.00) n = 29	3.62 (1.35, 3.11;4.13) 4.00 (1.00- 6.00) n = 29	**<.0001**
12 months	1.93 (0.94, 1.56;2.29) 2.00 (1.00- 4.00) n = 28	2.81 (1.55, 2.20;3.43) 3.00 (1.00- 6.00) n = 27	**0.038**
22 months	1.92 (1.75, 1.20;2.64) 1.00 (1.00- 9.00) n = 25	1.95 (1.00, 1.51;2.40) 2.00 (1.00- 4.00) n = 22	0.30
Scarring			
3 months	2.41 (0.95, 2.05;2.77) 2.00 (1.00- 5.00) n =29	4.48 (1.79, 3.80;5.16) 5.00 (1.00- 7.00) n =29	**<.0001**
12 months	2.11 (1.20, 1.64;2.57) 2.00 (1.00- 5.00) n = 28	3.64 (1.79, 2.95;4.34) 4.00 (1.00- 7.00) n = 28	**0.001**
22 months	2.28 (1.67, 1.59;2.97) 2.00 (1.00- 9.00) n = 25	2.23 (1.07, 1.75;2.70) 2.00 (1.00- 5.00) n = 22	0.66
Skin colour			
3 months	3.17 (1.23, 2.71;3.64) 3.00 (1.00- 7.00) n = 29	3.86 (1.27, 3.38;4.35) 4.00 (1.00- 6.00) n =29	**0.020**
12 months	2.36 (0.99, 1.97;2.74) 2.00 (1.00- 4.00) n = 28	3.25 (1.40, 2.71;3.79) 4.00 (1.00- 6.00) n = 28	**0.013**
22 months	2.24 (1.79, 1.50;2.98) 2.00 (1.00- 9.00) n = 25	2.23 (1.23, 1.68;2.77) 2.00 (1.00- 5.00) n = 22	0.61

	MIPS (n = 33)	LITT-P (n = 30)	*p*-value
Indentation			
3 months	2.34 (1.01, 1.96;2.73) 2.00 (1.00- 5.00) n = 29	4.00 (1.63, 3.38;4.62) 4.00 (1.00- 7.00) n =29	**<.0001**
12 months	2.26 (1.26, 1.76;2.76) 2.00 (1.00- 5.00) n = 27	3.33 (1.80, 2.62;4.04) 3.00 (1.00- 7.00) n = 27	**0.024**
22 months	2.50 (2.40, 1.49;3.51) 1.00 (1.00- 9.00) n = 24	2.23 (1.69, 1.48;2.98) 2.00 (1.00- 7.00) n = 22	0.85
Overall cosmetic score			
3 months	8.45 (0.74, 8.17;8.73) 8.00 (7.00- 10.00) n = 29	7.17 (1.20, 6.72;7.63) 7.00 (6.00- 10.00) n = 28	**<.0001**
12 months	8.14 (2.21, 7.29;9.00) 9.00 (1.00- 10.00) n = 28	7.50 (1.75, 6.82;8.18) 7.00 (1.00- 10.00) n = 28	**0.014**
22 months	7.96 (1.95, 7.16;8.76) 9.00 (2.00- 10.00) n = 25	7.68 (1.70, 6.93;8.44) 8.00 (2.00- 10.00) n = 22	0.20
Satisfaction with result without processor			
3 months	8.42 (1.47, 7.83;9.02) 9.00 (4.00- 10.00) n = 26	8.61 (1.29, 8.11;9.11) 9.00 (6.00- 10.00) n = 28	0.75
12 months	8.20 (1.38, 7.63;8.77) 9.00 (5.00- 10.00) n = 25	8.64 (1.25, 8.16;9.13) 8.50 (6.00- 10.00) n = 28	0.30
22 months	8.25 (1.96, 7.42;9.08) 9.00 (3.00- 10.00) n = 24	8.41 (1.53, 7.73;9.09) 8.50 (3.00- 10.00) n = 22	0.93
Satisfaction with result with processor			
3 months	7.41 (2.58, 6.39;8.43) 8.00 (1.00- 10.00) n = 27	7.89 (1.83, 7.18;8.60) 8.00 (3.00- 10.00) n = 28	0.73
12 months	7.52 (2.54, 6.47;8.57) 8.00 (1.00- 10.00) n = 25	7.96 (2.05, 7.17;8.76) 8.00 (1.00- 10.00) n = 28	0.72

	MIPS (n = 33)	LITT-P (n = 30)	*p*-value
22 months	7.39 (2.52, 6.30;8.48) 8.00 (2.00- 10.00) n = 23	7.90 (1.58, 7.19;8.62) 8.00 (4.00- 10.00) n = 21	0.80
Secondary outcome: soft tissue			
Mean skin level			
9 days	4.73 (1.66, 4.14;5.33) 5.00 (0.00- 7.25) n = 32	5.53 (1.15, 5.09;5.96) 5.50 (3.00- 7.25) n = 29	0.052
3 weeks	4.54 (1.58, 3.97;5.11) 5.00 (0.00- 7.00) n = 32	4.95 (1.05, 4.56;5.34) 5.00 (3.00- 7.00) n = 30	0.33
3 months	5.02 (1.42, 4.48;5.56) 5.00 (2.75- 8.00) n =29	5.08 (1.04, 4.68;5.47) 5.00 (2.50- 7.50) n = 29	0.64
12 months	5.10 (1.76, 4.42;5.78) 5.00 (1.00- 8.00) n = 28	5.52 (1.16, 5.06;5.98) 5.50 (3.50- 8.00) n = 27	0.43
22 months	5.04 (1.84, 4.30;5.78) 4.75 (1.00- 9.00) n = 26	5.26 (1.32, 4.71;5.81) 5.00 (2.50- 8.50) n =25	0.52
Skin sagging in any quadrant			
9 days	7 (21.2 %)	15 (51.7 %)	**0.024**
3 weeks	11 (34.4 %)	21 (70.0 %)	**0.010**
3 months	8 (27.6 %)	20 (71.4 %)	**0.002**
12 months	9 (32.1 %)	16 (57.1 %)	0.11
22 months	6 (23.1 %)	13 (52.0 %)	0.064
Wound dehiscence			
9 days	16 (48.5 %)	22 (33.3 %)	0.078
3 weeks	4 (12.5 %)	4 (13.3 %)	1.00
3 months	1 (3.3 %)	0 (0.0 %)	1.00
12 months	1 (3.6 %)	0 (0.0 %)	1.00
22 months	0 (0.0 %)	0 (0.0 %)	1.00
Soft tissue overgrowth			
Abutment changes	3 (9.1 %)	3 (10.0 %)	1.00
Revision surgery	2 (6.1 %)	1 (3.3 %)	1.00
Secondary outcome: implant extrusion			
Implant loss	5 (15.2 %)	1 (3.3 %)	0.12

Secondary Outcomes

Pain and Sensibility.

During a complete follow-up of 22 months, there were no significant differences in the presence of pain around the implant, radiating pain, and/or headache related to the BCD. At 3 weeks and subsequent follow-up, the mean pain scores were <2 of 10. The loss of sensibility was significantly less in the MIPS cohort in comparison with the LITT-P group for the follow-up visits until 3 months after surgery in the ITT population. No differences in loss of sensibility were found at 12- and 22-month follow-ups for either the ITT or PP population (Table 2, Supplementary Table 2).

Cosmetic Outcomes.

The outcomes of natural skin position, the extent of baldness, scarring, skin color, indentation, and overall cosmetic score (as assessed by the surgeon and subject) were significantly better in the MIPS group at 3 months and 1-year follow-up (Table 2, Supplementary Table 2). There were no differences between the surgical techniques at 22 months of follow-up except for the overall cosmetic score in the PP population ($p < 0.01$). The patient satisfaction in cosmetics with the result with (and without) processor attached did not differ between the two groups, and all scores were generally favorable during complete follow-up. An overview of the cosmetic results is presented in Table 2, Supplementary Table 2.

Soft Tissue Outcomes.

Skin sagging was generally significantly more present in patients who underwent the LITT-P compared with MIPS at different time points during the follow-up of 22 months (in the first 3 months for the ITT population and during the complete follow-up in the PP population) (Table 2, Supplementary Table 2). The mean skin level, measured as the distance between the top of the abutment to the skin in four quadrants, did not significantly differ between the two techniques during the follow-up. Also, the incidence of soft tissue overgrowth requiring abutment change or revision surgery was rare and did not differ between the groups. Abutment change was necessary for two patients (both in the LITT-P cohort), whereas four abutments were electively removed (one patient in the LITT-P cohort and the other three patients in the MIPS cohort). Revision surgery was performed in two patients in the MIPS group and one patient in the LITT-P group. The presence of wound dehiscence did not differ

between the groups during the follow-up. Table 2 and Supplementary Table 2 illustrate these soft tissue outcomes.

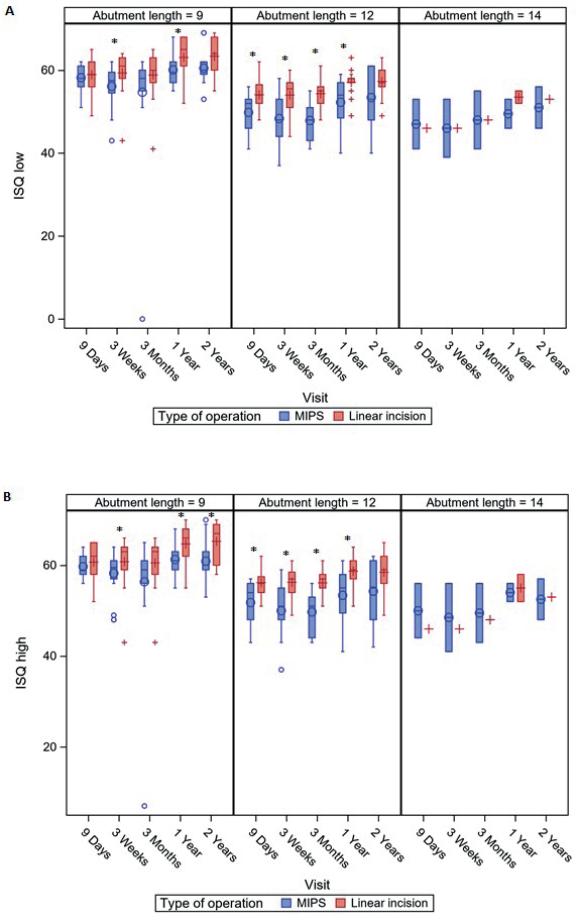
Implant Extrusion.

A total of six implants (9.5%) were extruded, with five implants (15.2%) in the MIPS group and one implant (3.3%) in the LITT-P group. The difference between the groups was not statistically significant [Kaplan–Meier analysis with log-rank test, the hazard ratio (95% confidence interval) = 4.71 (0.6–40.3) and p = 0.12]. The implant losses were registered between 26 and 99 days. In the MIPS group, three of five implants were lost spontaneously without previous signs of inflammation or pain, one implant was extruded after minor trauma, and one implant was lost after an episode of recurrent soft tissue inflammation (Holgers ≥ 2, despite local and systemic antibiotic treatment). The extruded implant in the LITT-P group was also lost after recurrent soft tissue inflammation (despite local and systemic treatment). For four of the six extruded implants, there was a decline in ISQ measures in consecutive postoperative visits before implant loss. There was no relation between extrusion rate and abutment lengths (three abutments of 9 mm and also three abutments of 12 mm).

Implant Stability Quotient.

No significant differences in ISQ low and high after implantation of the BCD were seen between the two different surgical approaches. An additional analysis, correcting for abutment length, showed that LITT-P patients had significantly higher ISQ low and ISQ high over time compared with patients after the MIPS procedure (Figure 3, Supplementary Figure 2).

Figure 3. Boxplots of ISQ measurements during standard follow-up visits with a subdivision for different abutment lengths. ISQ measurements are displayed for ISQ Low (A) en ISQ High (B). An asterisks (*) indicates a significant difference as calculated with a Mann-Whitney U-test (level of significance $p < 0.05$). The last visit ('2 years') was at 22 months of follow-up.



Tertiary Outcomes

The questionnaires HUI-III, APHAB, and ICECAP-A were used to assess the impact on hearing specific and general quality of life and capabilities (Supplementary Figure 3). In the HUI-III, the subjects who underwent the LITT-P had a significantly better single attribution score for pain (at 12- and 22-month follow-up and compared with the preoperative baseline at 22-month follow-up) and a lower score for vision (compared with preoperative baseline at 12- and 22-month follow-up). No differences in overall sum score and other single attribution

scores were found between the groups during follow-up. The APHAB and ICECAP-A did not reveal any significant difference in respectively global score (or any subdomains) and tariff value (or any life domains) between the MIPS and LITT-P cohort. An overview of the results at 22-month follow-up is shown in Supplementary Figure 3.

Discussion

In this multicenter randomized controlled trial, a comparison of the surgical outcomes is made between the MIPS technique and the LITT-P approach with a follow-up of 22 months. There were no differences in the presence of (adverse) soft tissue reactions between these techniques during complete follow-up. Also, no differences in pain related to the implant, wound dehiscence, mean skin level, soft tissue overgrowth, and overall quality of life were found between the groups. However, the outcomes for loss of sensibility (until 3-month post-surgery), cosmetic scores, and skin sagging were better in the MIPS cohort. Furthermore, the ISQ was higher in the LITT-P cohort for different abutment lengths at various times during follow-up. Finally, a nonsignificantly higher rate of implant extrusion was found after the MIPS procedure compared with the LITT-P procedure (15.2 vs. 3.3%).

Over the past few years, the punch-only techniques have been developed because of the minimally invasive nature of the surgery with possibly associated benefits. The short-term results were promising with improved outcomes on cosmetic appearance, skin sagging, sensibility loss, and surgical time without registration of more soft tissue problems in comparison with other current implantation techniques. Nevertheless, implant extrusion was mentioned several times as a warrant for further research[29-33,35,39]. Also, there were limited long-term results with only one small cohort study[36]. Moreover, a standardized procedure was lacking. In this context, the MIPS provided a clear, structured procedure, including a surgical kit.[33] To our knowledge, this is the first multicenter randomized controlled trial using the standardized MIPS with a long-term follow-up. Other strengths of this study are the large sample size (n = 63), no differences in implant type between the groups, and combining both relevant clinical and patient-related outcomes (including objective and subjective measures). Also, the strict registration of adverse events conform to protocol during both standard and extra visits, could lead to a more reliable reflection of (the number of) complications.

The primary outcome measure of this study is soft tissue reaction. There is a relatively higher prevalence of adverse soft tissue reactions and Holgers grade 3 for both techniques in this study in comparison with previous studies into tissue preservation techniques (for review, see Verheij et al.[7]). Possible explanations can be the relatively long follow-up of this study, the strict adherence to the protocol, and also the interobserver variability of the Holgers index[6]. Regarding the other soft tissue outcomes, there was less skin sagging after the MIPS operation compared with after LITT-P, possibly as a result of less soft tissue mobilization during MIPS surgery. Also, the extent of skin sagging may be influenced by soft tissue manipulation after the LITT-P procedure due to placement of the implant slightly lateral to the incision. Nonetheless, the adverse soft tissue reactions, maximum Holgers index, wound dehiscence, mean skin level, and soft tissue overgrowth did not differ between both techniques.

The pain scores showed no differences between the techniques and were generally low in this study. However, the single attribution score for pain in the quality of life questionnaire HUI-III was significantly better in the LITT-P cohort. The much broader definition of pain could explain this discrepancy in the context of quality of life. Because the pain scores related to the BCD (as judged by the patients) are generally low and not different between both techniques, it is not likely that this difference in the HUI- III could be attributed to the surgical technique. Finally, it is relevant to mention in this context that more invasive implantation techniques, such as the LITT-R and Dermatome technique, also have favorable pain scores (i.e., most patients experience no or only mild pain).[8,22]

Although sensibility loss was less in the MIPS cohort until 3 months of follow-up, no difference in sensibility loss was found at long-term follow-up. This can be related to the improvement of cutaneous sensibility after 1-year post-surgery, which is in accordance with other surgeries, such as otoplasty.[40] Similar results have been reported in another study comparing MIPS with LITT-P, where there was a tendency for better sensibility outcome after surgery and with the comparable outcome at 6 months; however, in subjective numbness, the MIPS technique was significantly better.[39] Potentially, this could reflect a process of regenerating (sensible) nerve units. The cosmetic outcomes as assessed by the surgeon were relatively favorable in both techniques; however, the results were better in the MIPS cohort. This is in line with the study of Caspers et al.[39]. Nevertheless, although there were these differences, patient satisfaction of the cosmetic results with (or without) processor did not differ between the

groups. This leads to the discussion that one could argue about the relevance of the better cosmetic results (as scored by the surgeon) of the MIPS in the decision-making for one of the techniques.

The ISQ measure is used as an indicator for implant stability. Because abutment length is known to influence ISQ measures[41] (as also confirmed by our data), a subanalysis demonstrated significantly higher ISQ values in the LITT-P cohort for different abutment lengths at various time points during follow-up compared with the MIPS cohort. In the current literature, the clinical relevance of the difference in ISQ value and its link to osseointegration are being discussed.[41,42] The individual absolute ISQ values for a particular implant system, leading to success or failure, are unknown. However, the trend in ISQ over time might be indicative of implant-bone stability for an individual implant.[41] Nevertheless, the usefulness of individual ISQ measures is still unknown.[41] Moreover, specifically regarding this study, previous literature did observe already lower ISQ values after MIPS surgery, which has been associated with the slightly different osteotomy shape.[43] Nonetheless, the indication of better osseointegration with these higher ISQ values after the LITT-P cannot be excluded. In addition, although statistically nonsignificant, there was more implant loss in the MIPS cohort. Less or delayed osseointegration as a possible factor could also not be excluded and might explain the rate of implant loss in our MIPS cohort, which is relatively high compared with previous studies.[5,7,44]

Other explanations for nonsignificantly more implant extrusions after the MIPS compared with LITT-P in this study can be postulated. First of all, the visibility at the implant site during surgery is reduced for MIPS compared with an open approach. This lack of exposure can lead to incomplete and/or angulated insertion.[30,35] Secondly, the smaller incision and the guided drill approach may result in reduced access for external irrigation to the osteotomy. Inadequate irrigation is a risk for excessive heat generation during drilling.[35,45] Previous researches, mainly in dental surgery, have shown that heat generation negatively affects the bone/osseointegration at the implant site. Depending on the amount of heat generated, it is possible that the bony turnover can be impaired due to necrosis, osteocytic degeneration, fibrosis, and increased osteoclastic activity. Besides external irrigation, there are different other factors influencing heat generation: operator (e.g., pressure, speed, and duration of drilling), equipment (e.g., design and sharpness of the drill), and patient-related facets (e.g.,

age, bone density, and implant location).[45,46] Possible solutions for this issue of heat generation may be improved drill systems that allow for better irrigation (including alteration in the shape of the drill and/or in the field of irrigation with the addition of internal irrigation). Also, the awareness of surgeons that the increase in temperature is directly proportional to the duration of drilling is important.[46,47]

In a recent bench study, the heat generation when drilling in artificial bone with the MIPS drill system and the conventional system for an open approach were compared.[47] The study confirmed that for both systems, when used according to the recommended and uncompromised clinical protocol, the heat generation was below the threshold for thermally induced damage. Interestingly, the study revealed that the MIPS system was less sensitive to a reduction of the irrigation, whereas it was much more sensitive to a prolonged drilling procedure, indicating an important contribution of the operator performing the drilling procedure.[47]

A third explanation of the impaired osseointegration might be soft tissue entering the drill hole despite using a cannula, which may lead to entrapment of soft tissue fragments in the osteotomy when inserting the implant. These hypotheses mentioned earlier may imply the need for advanced clinical experience when using the MIPS approach. In correspondence with the findings using flapless dental implant placement techniques, there seems to be a learning curve to achieve treatment success. A learning curve for the MIPS technique could potentially also be a prerequisite for adequate implantation.[48-50] For example, surgeons with more experience in BCD surgery may encounter fewer difficulties with limited vision during implantation. Also, a more routine and faster procedure will reduce the drilling time and thus thermal damage to the implant site. Training and adherence to the instructions and cautions seem relevant for the success of the procedure. Although this was stated already previously[33,35], the present study did not find any learning effects based on our adverse events log, potentially resulting from including only experienced surgeons.

Finally, the quality of life was assessed in this study with not only a hearing-specific questionnaire (APHAB)[51] but also a health status classification questionnaire (HUI- III)[52] and a capability measure (ICECAP-A)[53]. There were no differences in overall quality of life between both cohorts during follow-up. This multi-domain evaluation of the quality of life is an

extra-strength of this study because it tells us something about the impact of our primary and secondary outcomes on a patient's functioning in their daily life. In fact, the relevance of the primary and secondary results for patients might be discussed if the quality of life between the groups does not differ. This could mean that the differences found in clinical outcomes may not be important factors in the opinion of the patients in the population. On the other hand, one might argue about the validity of the questionnaires for this intervention. Perhaps, more procedure-related questionnaires might be more sensitive.

Although the various strengths of the current study, the limitations of this study should be considered when interpreting the results. Firstly, all surgeons had a long time of experience with the linear incision technique. In contrast, the MIPS is a relatively new technique with a learning curve. However, as we did not find any learning effects, it is unlikely that this influenced our data. Secondly, some outcome measures regarding soft tissue problems and cosmetics imply an interobserver variability, which could have influenced the results. The fact that the surgeons and researcher could not be blinded might attribute to this point. Finally, as already described in the 3-month follow-up results[32], the study population was of Caucasian origin. It has previously been indicated that the risk of soft tissue problems after BCD surgery (particularly scar formation) is higher in the African-American population.[54]

In conclusion, these long-term results show favorable outcomes for both techniques regarding soft tissue reactions, pain, patient satisfaction, and quality of life. The MIPS has better outcomes in the context of skin sensibility (on short-term results), cosmetic appearance, and skin sagging in comparison with the LITT-P. In combination with the previously described significantly shorter surgical time[35], MIPS is a promising technique. Nevertheless, as demonstrated in the discussion, the results show concerns regarding osseointegration and implant extrusion after the MIPS procedure. Possibly, this might be explained by less exposure during the procedure with more risk on angulated insertion, prolonged drilling time, inadequate irrigation, and the need for gaining surgical experience. However, after 3 months of follow-up, no implants were lost. Future developments in irrigation, drilling systems, and optimized standardized surgical procedures and training may overcome these problems and should be a focus for further research.

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Supplementary Material

Supplementary Table 1. Baseline characteristics per protocol population.

Baseline characteristic	MIPS (n = 21)	LITT-P (n = 17)	*p*-value
Age (years)			
Mean (SD), 95 %- CI	52.1 (15.1), 45.3; 59.0	51.0 (17.3), 42.1; 59.9	0.83
Median (Min- Max)	53.0 (30.0- 80.0)	52.0 (24.0- 75.0)	
Gender			
Male	8 (38.1 %)	7 (41.2 %)	1.00
Female	13 (61.9 %)	10 (58.8 %)	
Type of hearing losse			
Acquired conductive/mixed hearing loss	16 (76.2 %)	16 (94.1 %)	
Single sided deafness	4 (19.0 %)	1 (5.9 %)	0.30
Congenital conductive hearing loss	1 (4.8 %)	0 (0.0 %)	
Smoking			
Yes	3 (14.3 %)	4 (23.5 %)	0.75
No	18 (85.7 %)	13 (76.5 %)	
Body Mass Index (BMI; kg/m2)			
Mean (SD), 95 %- CI	27.7 (6.5), 24.7; 30.7	28.1 (4.7), 25.6; 30.7	0.62
Median (Min- Max)	27.2 (20.5- 44.4)	27.0 (22.0- 36.3)	
Ethinicity			
Caucasian	21 (100.0 %)	17 (100.0 %)	
Implantation site			
Right	13 (61.9 %)	7 (41.2 %)	0.34
Left	8 (38.1 %)	10 (58.8 %)	
Abutment length			
9	14 (66.7 %)	8 (47.1 %)	0.224
12	5 (23.8 %)	9 (52.9 %)	0.064
14	2 (9.5 %)	0 (0.0 %)	

Supplementary Table 2. Primary and secondary outcomes (PP population). Continuous variables are presented as mean (SD, 95% CI) and median (min- max). The n is showed at 22 months follow-up visits and otherwise if it differs from the PP population numbers. A significant p-value ($p < 0.05$) is showed in bold.

Pain is graded in a 10-point scale with a scale of 0 representing absence of pain to 10 representing the worst pain. The area of sensibility loss is registered as the most outward diameter from abutment (in mm). The cosmetic observed variables are rated as 1 being no difference with the healthy contralateral site and with 10 being the most negative difference with the healthy situation. Only the overall cosmetic score and patient satisfaction will be rated with 10 being the best cosmetic result. The skin level is measured as the distance between the top of the abutment to the skin in four quadrants (in mm).

	MIPS (n = 21)	**LITT-P (n = 17)**	***p*-value**
Primary outcome: (adverse) soft tissue reactions			
Adverse soft tissue reaction (Holgers ≥ 2) from surgery to 22months	5 (23.8 %)	8 (47.1 %)	0.13
Adverse soft tissue reaction (Holgers ≥ 2) from surgery to 22 months (with the Fisher's Exact Test)	5 (23.8 %)	8 (47.1 %)	0.25
Maximum Holgers Index at standard and extra visits			
0 No irritation	6 (28.6 %)	1 (5.9 %)	
1 Slight redness	10 (47.6 %)	8 (47.1 %)	
2 Red and slightly moist tissue	2 (9.5 %)	7 (41.2 %)	
3 Reddish and moist tissue, sometimes granulation formation	3 (14.3 %)	1 (5.9 %)	0.20
4 Profound signs of infection resulting in implant removal	0 (0.0 %)	0 (0.0 %)	
Secondary outcome: pain			
Pain around the implant			
9 days	1.71 (2.05, 0.78;2.65) 1.00 (0.00- 6.00)	2.41 (2.72, 1.01;3.81) 2.00 (0.00- 8.00)	0.43
3 weeks	0.952 (1.284, 0.368;1.537) 0.00 (0.00- 4.00)	0.647 (1.115, 0.074;1.220) 0.00 (0.00-3.00)	0.34
3 months	1.52 (2.02, 0.61;2.44) 0.00 (0.00- 6.00)	0.941 (1.638, 0.099;1.1783) 0.00 (0.00- 5.00)	0.24
12 months	0.952 (1.936, 0.071;1.834) 0.00 (0.00- 6.00)	1.53 (2.48, 0.26;2.80) 0.00 (0.00- 8.00)	0.44
22 months	0.400 (0.821, 0.016;0.784) 0.00 (0.00- 2.00) n = 20	0.941 (1.749, 0.042;1.840) 0.00 (0.00- 5.00) n = 17	0.43

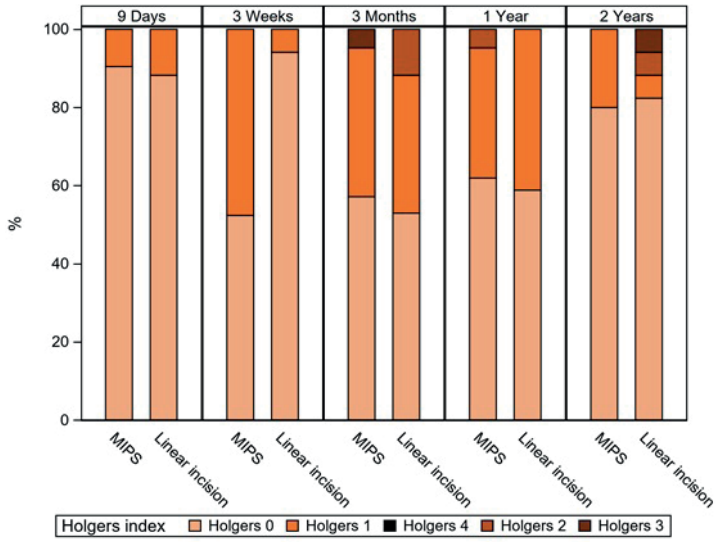
	MIPS (n = 21)	LITT-P (n = 17)	*p*-value
Radiating pain from the implant			
9 days	0.810 (1.965,-0.085;1.704) 0.00 (0.00- 7.00)	0.824 (2.038,-0.224;1.871) 0.00 (0.00- 8.00)	0.80
3 weeks	0.667 (1.592,-0.058;1.391) 0.00 (0.00- 5.00)	0.176 (0.728,-0.198;0.551) 0.00 (0.00- 3.00)	0.24
3 months	0.762 (1.814,-0.064;1.588) 0.00 (0.00- 6.00)	0.529 (1.505,-0.244;1.303) 0.00 (0.00- 5.00)	0.39
12 months	0.381 (1.244,-0.185;0.947) 0.00 (0.00- 5.00)	0.294 (1.213,-0.329;0.918) 0.00 (0.00- 5.00)	0.73
22 months	0.200 (0.894,-0.219;0.619) 0.00 (0.00- 4.00) n = 20	0.294 (0.849,-0.142;0.731) 0.00 (0.00- 3.00) n =17	0.52
Headache related to the BCD			
9 days	0.667 (1.713,-0.113;1.446) 0.00 (0.00- 7.00)	1.29 (2.28, 0.12;2.47) 0.00 (0.00- 7.00)	0.40
3 weeks	0.571 (1.805,-0.250;1.393) 0.00 (0.00- 6.00)	0.118 (0.485,-0.132;0.367) 0.00 (0.00-2.00)	0.66
3 months	0.905 (2.322,-0.152;1.962) 0.00 (0.00- 8.00)	0.412 (1.064,-0.135;0.959) 0.00 (0.00- 4.00)	0.96
12 months	0.381 (1.359,-0.238;1.000) 0.00 (0.00- 6.00)	0.00 (0.00, 0.00;0.00) 0.00 (0.00- 0.00)	0.21
22 months	0.00 (0.00, 0.00;0.00) 0.00 (0.00- 0.00) n = 20	0.412 (1.698,-0.461;1.285) 0.00 (0.00- 7.00) n = 17	0.30
Secondary outcome: sensibility			
Area loss of sensibility (most outward diameter from abutment in mm)			
9 days	3.67 (7.47, 0.27;7.07) 0.00 (0.00- 25.00)	12.8 (14.6, 5.3;20.3) 15.0 (0.0- 50.0)	**0.022**
3 weeks	0.333 (1.155,-0.192;0.859) 0.00 (0.00- 5.00)	4.24 (10.15,-0.98;9.46) 0.00 (0.00- 35.00)	0.21
3 months	0.095 (0.436,-0.103;0.294) 0.00 (0.00- 2.00)	2.82 (6.61,-0.57;6.22) 0.00 (0.00- 25.00)	0.080
12 months	0.048 (0.218,-0.052;0.147) 0.00 (0.00- 1.00)	1.71 (4.84,-0.79;4.20) 0,00 (0.00- 18.00)	0.20

		MIPS (n = 21)	LITT-P (n = 17)	*p*-value
22 months		1.18 (4.85,-1.32;3.67) 0.00 (0.00- 20.00) n = 17	0.00 (0.00, 0.00;0.00) 0.00 (0.00- 0.00) n = 14	0.40
Presence of loss of sensibility?				
9 days	No	16 (76.2 %)	7 (41.2 %)	0.062
	Yes	5 (23.8 %)	10 (58.8 %)	
3 weeks	No	19 (90.5 %)	13 (76.5 %)	0.47
	Yes	2 (9.5 %)	4 (23.5 %)	
3 months	No	20 (95.2 %)	13 (76.5 %)	0.22
	Yes	1 (4.8 %)	4 (23.5 %)	
12 months	No	20 (95.2 %)	14 (82.4 %)	0.45
	Yes	1 (4.8 %)	3 (17.6 %)	
22 months	No	16 (94.1 %)	14 (100.0 %)	1.00
	Yes	1 (5.9 %)	0 (0.0 %)	
Secondary outcome: cosmetic appearance				
Natural skin position				
3 months		2.81 (1.12, 2.30;3.32) 3.00 (1.00- 5.00)	3.71 (1.40, 2.98;4.43) 3.00 (1.00- 6.00)	**0.048**
12 months		2.14 (1.15, 1.62;2.67) 2.00 (1.00- 5.00)	3.06 (1.25, 2.42;3.70) 3.00 (1.00- 5.00)	**0.014**
22 months		1.94 (1.66, 1.12;2.77) 1.50 (1.00- 8.00) n = 18	2.50 (1.87, 1.42;3.58) 2.00 (1.00- 7.00) n = 14	0.28
Extent of baldness				
3 months		2.24 (0.83, 1.86;2.62) 2.00 (1.00- 4.00)	4.00 (1.32, 3.32;4.68) 4.00 (1.00- 6.00)	**<.0001**
12 months		1.95 (0.92, 1.53;2.37) 2.00 (1.00- 4.00) n = 21	3.25 (1.34, 2.54;3.96) 3.50 (1.00- 5.00) n = 16	**0.0037**
22 months		1.94 (1.95, 0.97;2.92) 1.00 (1.00- 9.00) n = 18	2.21 (1.12, 1.57;2.86) 2.00 (1.00- 4.00) n = 14	0.15
Scarring				
3 months		2.38 (1.02, 1.92;2.85) 2.00 (1.00- 5.00)	4.94 (1.60, 4.12;5.76) 5.00 (1.00- 7.00)	**<.0001**
12 months		2.14 (1.24, 1.58;2.71) 2.00 (1.00- 5.00)	4.06 (1.60, 3.24;4.88) 4.00 (1.00- 7.00)	**0.0006**

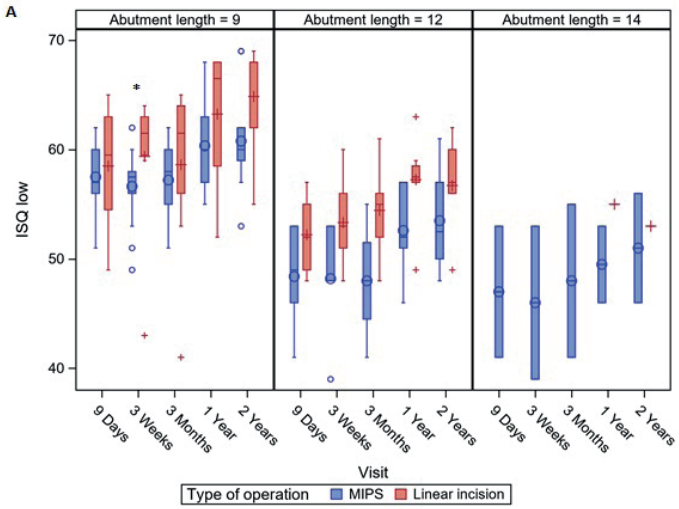
	MIPS (n = 21)	LITT-P (n = 17)	*p*-value
22 months	2.28 (1.87, 1.35;3.21) 2.00 (1.00- 9.00) n = 18	2.29 (1.20, 1.59;2.98) 2.00 (1.00- 5.00) n = 14	0.57
Skin colour			
3 months	3.10 (1.04, 2.62;3.57) 3.00 (1.00- 5.00)	4.24 (1.03, 3.70;4.77) 4.00 (3.00- 6.00)	**0.0047**
12 months	2.48 (1.08, 1.99;2.97) 2.00 (1.00- 4.00)	3.71 (1.21, 3.08;4.33) 4.00 (2.00- 6.00)	**0.0041**
22 months	2.11 (1.97, 1.13;3.09) 1.00 (1.00- 9.00) n = 18	2.64 (1.28, 1.91;3.38) 2.00 (1.00- 5.00) n = 14	0.065
Indentation			
3 months	2.24 (0.94, 1.81;2.67) 2.00 (1.00- 5.00)	4.12 (1.54, 3.33;4.91) 4.00 (1.00- 7.00)	**0.0002**
12 months	2.24 (1.22, 1.68;2.79) 2.00 (1.00- 5.00)	3.76 (1.68, 2.90;4.63) 4.00 (1.00- 7.00)	**0.0047**
22 months	2.06 (2.10, 1.01;3.10) 1.00 (1.00- 9.00) n = 18	2.50 (1.99, 1.35;3.65) 2.00 (1.00- 7.00) n = 14	0.26
Overall cosmetic score			
3 months	8.52 (0.75, 8.18;8.87) 8.00 (7.00- 10.00)	6.94 (1.09, 6.38;7.50) 7.00 (6.00- 9.00)	**<.0001**
12 months	8.81 (0.93, 8.39;9.23) 9.00 (7.00- 10.00)	7.41 (1.06, 6.86;7.96) 7.00 (5.00- 9.00)	**0.0003**
22 months	8.67 (0.84, 8.25;9.08) 9.00 (7.00- 10.00) n = 18	7.64 (1.08, 7.02;8.27) 8.00 (6.00- 9.00) n =14	**0.0078**
Satisfaction with result without processor			
3 months	8.37 (1.57, 7.61;9.13) 9.00 (4.00- 10.00) n =19	8.31 (1.45, 7.54;9.08) 8.00 (6.00- 10.00) n = 16	0.80
12 months	7.94 (1.55, 7.17;8.72) 8.00 (5.00- 10.00) n = 18	8.53 (1.18, 7.92;9.14) 8.00 (6.00- 10.00) n = 17	0.31
22 months	8.82 (1.29, 8.16;9.48) 9.00 (6.00- 10.00) n = 17	8.36 (0.93, 7.82;8.89) 8.00 (7.00- 10.00) n = 14	0.19

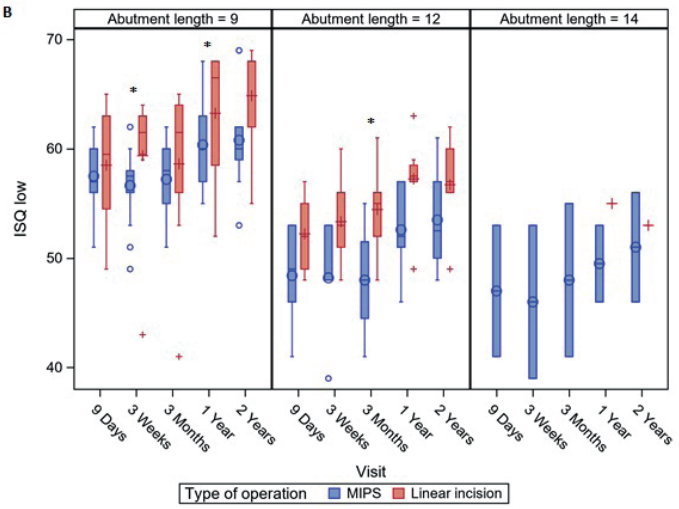
	MIPS (n = 21)	LITT-P (n = 17)	*p*-value
Satisfaction with result with processor			
3 months	7.37 (2.34, 6.24;8.50) 8.00 (1.00- 10.00) n = 19	7.71 (1.65, 6.86;8.55) 8.00 (5.00- 10.00) n = 17	0.94
12 months	7.39 (2.38, 6.21;8.57) 8.00 (3.00- 10.00) n = 18	8.00 (1.70, 7.13;8.87) 8.00 (5.00- 10.00) n = 17	0.55
22 months	7.41 (2.53, 6.11;8.71) 8.00 (3.00- 10.00) n = 17	7.23 (1.54, 6.30;8.16) 7.00 (4.00- 10.00) n = 13	0.60
Secondary outcome: soft tissue			
Mean skin level			
9 days	5.23 (1.15, 4.70;5.75) 5.75 (3.25- 7.25) n = 21	5.67 (0.90, 5.19;6.15) 5.75 (4.25- 7.25) n =16	0.25
3 weeks	4.99 (1.19, 4.44;5.53) 5.00 (3.00- 7.00)	5.06 (0.88, 4.61;5.51) 5.00 (3.25- 7.00)	0.82
3 months	5.31 (1.27, 4.73;5.89) 5.00 (3.00- 8.00)	5.24 (0.71, 4.87;5.60) 5.00 (4.00- 5.60)	0.98
12 months	5.56 (1.49, 4.88;6.24) 5.50 (3.00- 8.00)	5.54 (1.01, 5.03;6.06) 5.50 (4.00- 8.00)	1.00
22 months	5.56 (1.66, 4.79;6.34) 5.63 (3.00- 9.00) n = 20	5.79 (1.15, 5.20;6.38) 5.75 (4.00- 8.00) n = 17	0.62
Skin sagging in any quadrant			
9 days	4 (19.0 %)	8 (50.0 %)	0.10
3 weeks	5 (23.8 %)	15 (88.2 %)	**0.0002**
3 months	5 (23.8 %)	13 (76.5 %)	**0.0031**
12 months	5 (23.8 %)	11 (64.7 %)	**0.026**
22 months	4 (20.0 %)	11 (64.7 %)	**0.014**
Wound dehiscence			
9 days	12 (57.1 %)	13 (76.5 %)	0.37
3 weeks	2 (9.5 %)	2 (11.8 %)	1.00
3 months	0.0 (0.0 %)	0.0 (0.0 %)	1.00
12 months	0.0 (0.0 %)	0.0 (0.0 %)	1.00
22 months	0.0 (0.0 %)	0.0 (0.0 %)	1.00
Soft tissue overgrowth			
Abutment changes	2 (9.5 %)	2 (11.8 %)	1.00
Revision surgery	1 (4.8 %)	0 (0.0 %)	1.00

Supplementary Figure 1: Stacked bar chart for the highest observed Holgers Index scores during standard follow-up visits (PP analysis). The last visit ('2 years') was at 22 months of follow-up.



Supplementary Figure 2: Boxplots of ISQ measurements during standard follow-up visits with a subdivision for different abutment lengths (PP population). ISQ measurements are displayed for ISQ Low (A) en ISQ High (B). An asterisks (*) indicates a significant difference as calculated with a Mann-Whitney U-test (level of significance $p < 0.05$). The last visit ('2 years') was at 22 months of follow-up.



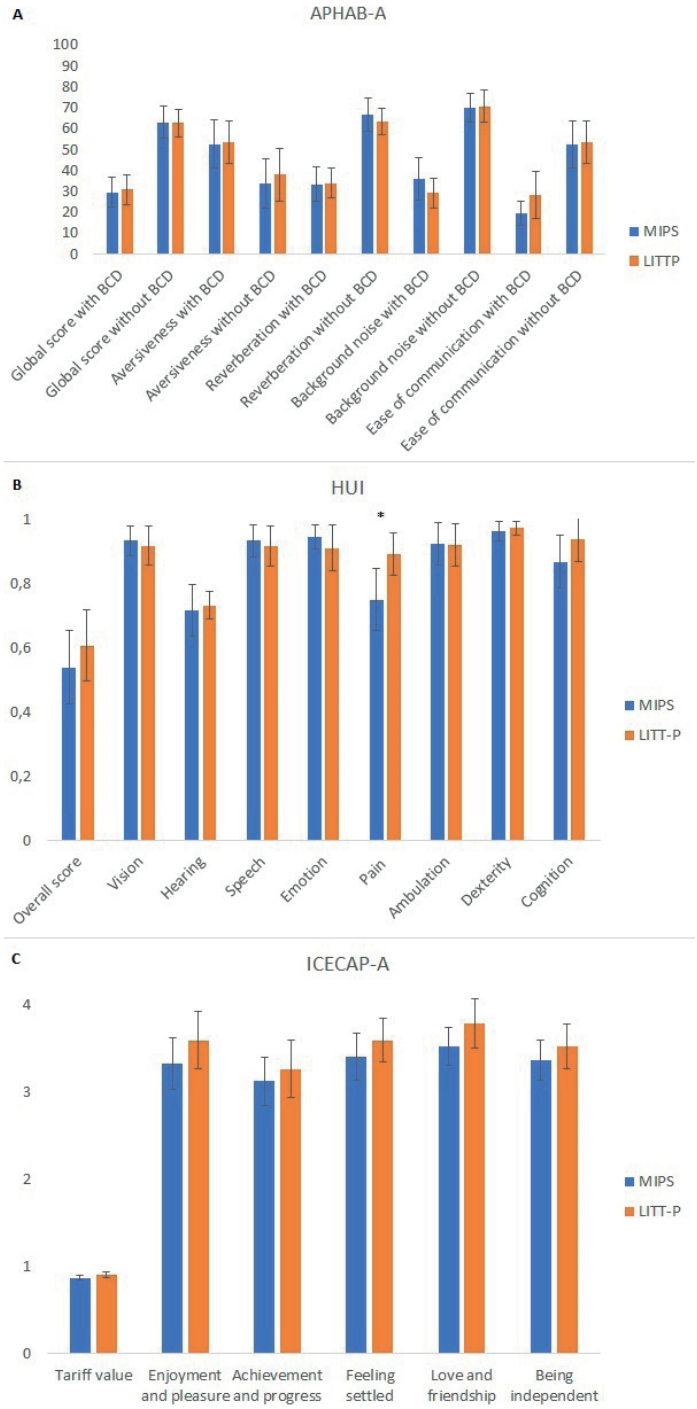


Supplementary Figure 3: Results of the quality of life questionnaires at 22 months follow-up (with 95 % confidence intervals). An asterisks (*) indicates a significant difference as calculated with a Mann-Whitney U-test (level of significance $p < 0.05$).

A. The Abbreviated Profile of Hearing Aid Benefit (APHAB) including the four subscales (with or without BCD). The scale 'Aversiveness' means the unpleasantness of environmental sounds. 'Reverberation' indicates the communication in reverberant surroundings. "Background noise' specifies the communication in spaces with high background noise levels. The sub-item 'Ease of communication' means the strain of communication under relatively favorable conditions. Finally, the 'global score' is calculated as the mean score of the subscales reverberation, background noise and ease of communication. The displayed mean score can vary between 1 and 99 % which show how frequent the subjects experience difficulties in (this field of) hearing performance.

B. The Health Utilities Index Mark III (HUI-III) including the single attribute utility functions. The displayed mean scores range from 0 to 1 with 1.00 indicating a perfect health status. The overall (utility) score is calculated based on the different weighted single attribute utility scores.

C. The ICEpop CAPability measure for Adults (ICECAP-A) which compromises five domains of capabilities: 'enjoyement and pleasure' (an ability to experience enjoyment and pleasure), 'achievement and progress' (an ability to achieve and progress in life), 'feeling settled' (an ability to feel settled and secure), 'love and friendship' (an ability to have love, friendship and support) and 'being independent' (an ability to be autonomous). The mean scores are presented with the 'top' level (full capability) takes the value '4' and the bottom level (no capability) takes the value '1'. Finally, the tariff value is calculated based on the different weighted individual attributes. This is an overall state of capability and ranges between 0 and 1 (with '1' as highest score for overall capability).


A
APHAB-A
100
90
80
70
60
50
40
30
20
10
0
MIPS
LITTP
Global score with BCD
Global score without BCD
Aversiveness with BCD
Aversiveness without BCD
Reverberation with BCD
Reverberation without BCD
Background noise with BCD
Background noise without BCD
Ease of communication with BCD
Ease of communication without BCD
B
HUI
*
1
0,8
0,6
0,4
0,2
0
MIPS
LITT-P
Overall score
Vision
Hearing
Speech
Emotion
Pain
Ambulation
Dexterity
Cognition
C
ICECAP-A
4
3
2
1
0
MIPS
LITT-P
Tariff value
Enjoyment and pleasure
Achievement and progress
Feeling settled
Love and friendship
Being independent

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6

EX VIVO EVALUATION OF A NEW DRILL SYSTEM FOR PLACEMENT OF PERCUTANEOUS BONE CONDUCTION DEVICES

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Frontiers in Surgery. 2022;9:858117.

Abstract

The procedure for installation of a percutaneous bone-conducting device has undergone significant improvements since its introduction 40 years ago. Today, the linear incision technique with tissue preservation (LITT-P) and the minimally invasive procedure (MIPS) are the most commonly used approaches. In both these techniques, a gradual increase of the osteotomy using a three-step drilling sequence is utilized, as this approach can allow a stepwise deepening and widening of the osteotomy in the mastoid and can prevent bone overheating. A new minimally invasive procedure (MONO) has been developed that allows an osteotomy to be performed and enables complete removal of the bone volume in one single drill step for a 4 mm implant using a novel parabolic twist drill. Here, the feasibility of the MONO procedure was qualitatively and quantitatively evaluated in terms of the dura response to drill trauma in comparison with the outcomes achieved with guide drills used for the LITT-P and MIPS techniques. Fresh frozen temporal bone from a human cadaver was subjected to penetration by three drills beyond the base of the mastoid bone to different depths. The sites were evaluated, and the damage to and possible penetration of the dura were determined. The results showed that for a drill depth exceeding mastoid bone thickness by not more than 1 mm, damage to the dura was limited or nonexistent, whereas for a drill depth exceeding bone thickness by 2 mm, damage increased, or the dura was penetrated. There was a trend toward more damage and penetration for both the round burr and MIPS guide drill compared with the MONO drill bit. From this experimental ex vivo study, it can be concluded that if the dura is encountered, the MONO system is not more inclined to penetrate the dura than the conventional LITT-P and MIPS systems.

Introduction

In recent decades, the dynamic field of percutaneous bone conduction devices (BCDs) has inspired researchers from around the world to improve these implants, their abutment designs and related surgical techniques. These osseointegrated BCDs were introduced by Tjellström in 1977 and were based on the principle of bone conduction hearing.[1] Currently, many people with hearing problems benefit from percutaneous BCDs, which is indicated for patients with uni- and bilateral conductive or mixed hearing loss (with an inability or intolerance to wear conventional hearing aids)[2,3] and patients with single-sided deafness[4].

The related surgical technique has evolved from a free retroauricular full-thickness skin graft[5] to pedicled grafts, the dermatome technique and a linear incision technique with tissue reduction (LITT-R)[6-8]. Although surgery was safe, adverse soft tissue reactions occurred.[6-9] This led to the development of less invasive surgical approaches where LITT-R was modified to a linear incision technique with soft tissue preservation (LITT-P)[10], leading to reduced soft tissue-related problems.[11-15] Moreover, more favorable results in terms of surgery time, cosmetic appearance and skin sensibility loss were registered.[12,15-19] Following the successful introduction of LITT-P, research has focused on further reducing the invasiveness of the surgical technique, e.g., by employing so-called punch-only techniques[20-23]. A further refinement of the punch-only technique is the minimally invasive Ponto surgery (MIPS), introduced by Oticon Medical AB (Askim, Sweden) in 2015. Here, the implant is installed using a standardized surgical kit including a cannula that is used as a guide during the drilling sequence.[24]

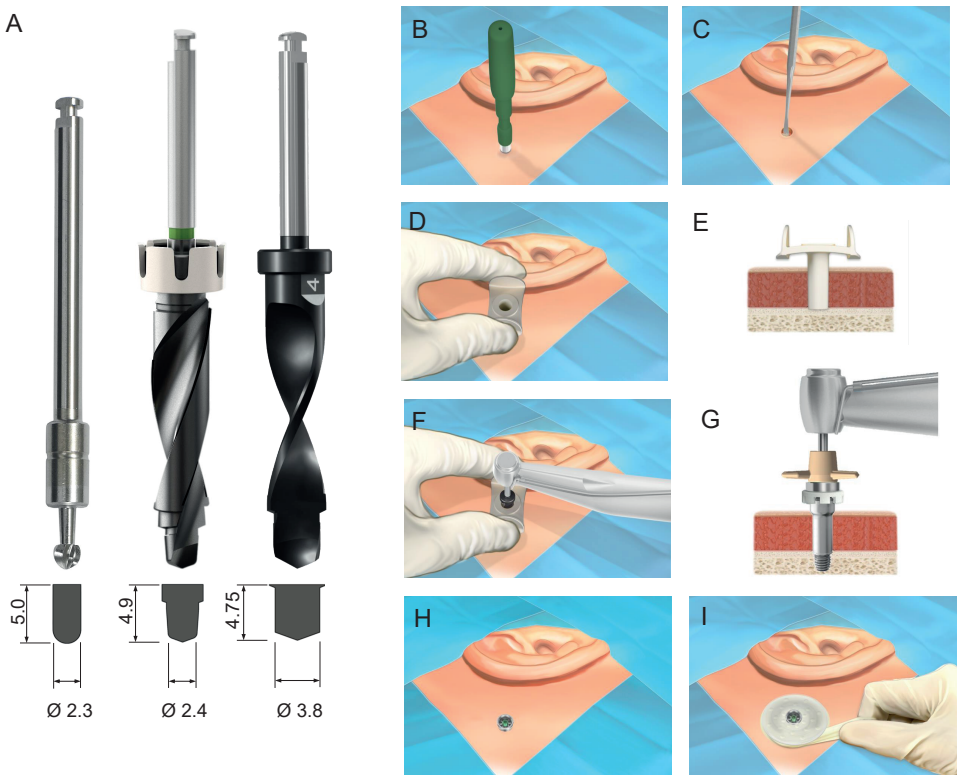
The results of the MIPS technique are encouraging, and several recent studies have compared the clinical outcome of MIPS with that of the commonly used LITT-P[25-29]. While both techniques show favorable soft tissue outcomes compared with the outcomes of previous tissue reduction approaches, MIPS is also associated with improvements in terms of surgery time, cosmetics and preservation of skin sensibility.[25-31] In addition to providing benefits to patients, improvements in clinical efficiency using MIPS have been reported in cost analysis studies.[32] While several studies have reported comparable implant survival rates for MIPS compared to LITT-P[27-29,31,33], lower implant survival for MIPS has also been reported[25,26,34]. Possible reasons can be the reduced visibility during the procedure, introducing a potential

risk of angulated insertion or interposing soft tissue. Additionally, as a result of the smaller incision and guided drilling, there is a potential risk for excessive heat generation followed by negative effects on osseointegration at the implant site[35]. Since the introduction of MIPS, the drill components in the surgical kit have been updated with the aim of reducing the heat generated during drilling[36]. A recent clinical study reported a trend toward an improved implant survival rate using this updated MIPS system in comparison with the original drill system.[37]

Similar to the linear incision technique, MIPS employs a three-step drilling protocol with initial penetration using the cannula guide drill to a depth of 3.9 mm.[38] If bone is present in the bottom of the osteotomy site, an additional 1 mm depth is created with the cannula guide drill, allowing the subsequent installation of a 4 mm long implant. To further optimize and simplify the drilling procedure, a novel drilling system, called the MONO procedure, has been developed in which the final osteotomy for a 4 mm implant is created in only one single drilling step, in contrast to the LITT-P and MIPS systems, where a three-step drilling sequence is employed (Figures 1A–I).[39,40] In this single drilling step, the total drilling depth was 4.75 mm. The possible advantages of the MONO procedure are less drilling time and heat generation and fewer negative effects on peri-implant bone and osseointegration. In cases where the temporal bone thickness at the implantation site is less than the total drilling depth, the dura will be exposed and possibly traumatized or penetrated by the drill bit. Hence, a relevant and important prerequisite for the success of the MONO system is to evaluate the behavior of the drill bit when encountering the dura. The bone thickness in the area of the implantation site of BCDs has been evaluated in scientific studies.[41,42] Baker et al. reported average bone thicknesses of 6.78 ± 2.06 mm and 6.90 ± 2.27 mm (mean± SD) in adult patients with and without chronic ear disease, respectively.[41] Kim et al. demonstrated that the average thickness was between 6.17 and 7.41 mm for patients aged 10 years or older. The study indicated that 95% of the adult population has a bone thickness of 5 mm or more in the area of the BCD position.[42] Therefore, based on these evaluations, the MONO drill system, where the drill depth is 4.75 mm, can be considered a safe approach in an adult population with normal bone anatomy. In contrast, for the LITT-P and MIPS systems, the initial penetration of the mastoid bone is 4 mm and 3.9 mm, respectively, with corresponding final penetration depths of 5 and 4.9 mm when a 4 mm implant is installed. Therefore, using

MONO, there is still a potentially higher risk for encountering the dura than with the LITT-P and MIPS systems.

Figure 1. (A) The three drill bits evaluated in the study: the guide drill used the Ponto linear incision technique (left), MIPS guide drill (middle) and MONO drill (right). Below each drill, the shape of the osteotomy site following the drilling sequence using the respective drill is shown. Measurements in millimeters. (B–I) The surgical protocol for implantation of a percutaneous bone conduction device using the MONO procedure. (B) The skin is incised with a 5 mm biopsy skin punch. (C) The periosteum is removed from the bone surface at the site. (D,E) The cannula is inserted in the circular incision. (F) Osteotomy is created in one single drill step using the MONO drill. (G,H) The cannula is removed, and the implant is installed. (I) A healing cap and dressing are applied. Images courtesy of Oticon Medical AB © 2021.



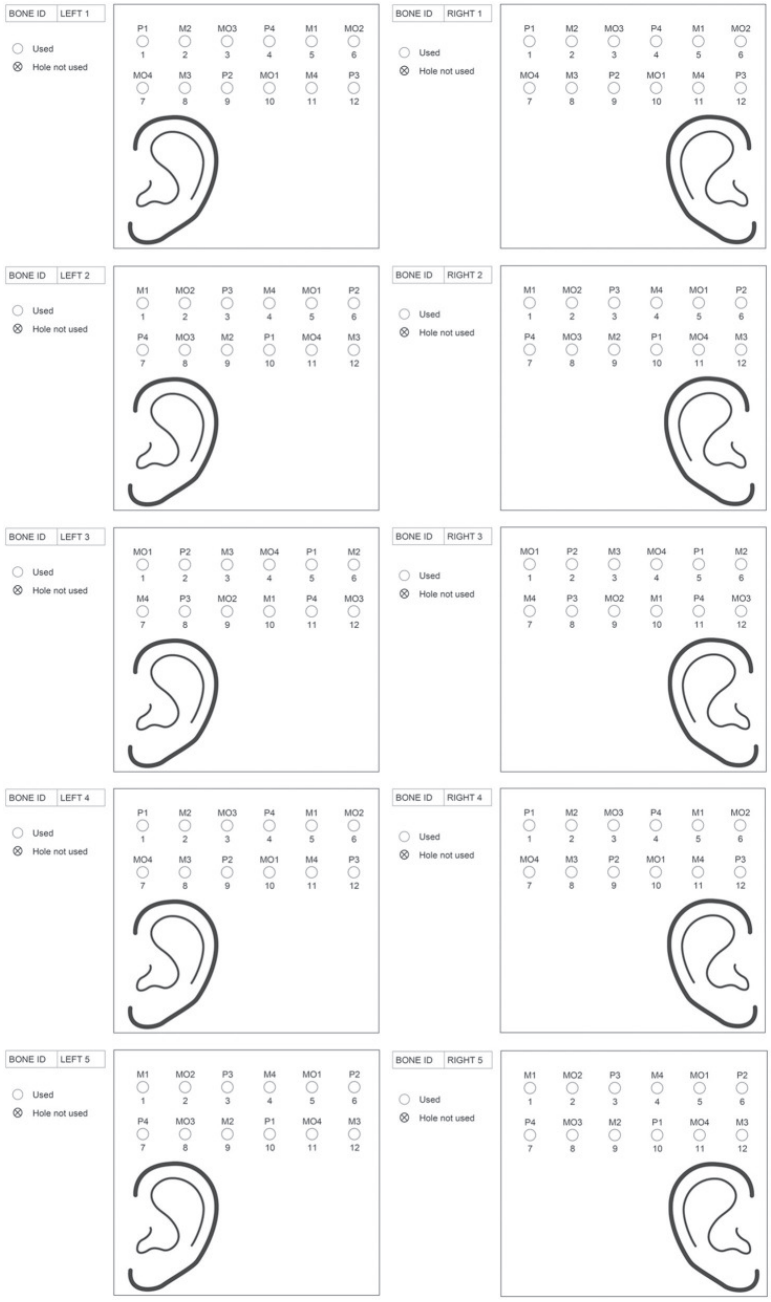
The objective of the current study was to qualitatively and quantitatively evaluate the dura response to drill trauma using the MONO drill in comparison with the outcomes achieved with guide drills used for the LITT-P and MIPS techniques.

Materials and Methods

Study Design

This was an ex vivo experimental study on cadaveric, fresh frozen, human temporal bone samples. Five temporal bone specimens were used with both right and left temporal bone samples (i.e., a total of ten temporal bone samples). The damage and possible penetration of the dura in these specimens were compared between drill bits and penetration depths. Three different drill bits were evaluated: the guide drill for the LITT-P technique (designated Ponto, P), the guide drill for the MIPS system (MIPS, M) and the MONO drill (MONO, MO) (Figure 1A). Penetration depth (PD) was defined as the depth of drilling beyond the base of the temporal bone (Figure 3B). To reduce the influence of variation in temporal bone sample and position on the results, the drill sites for the different drills and penetration depths were rotated using a predetermined randomized schedule (Figure 2). Two drill operators performed the experiment (MLJ and AH) with an equal distribution of temporal bone specimens between them.

Figure 2. The predetermined randomized schedule with the drill sites for the different drills and penetration depths. The abbreviations used for the drilling systems are P = Ponto guide drill, M = MIPS guide drill and MO = MONO. The numbers behind the drilling systems indicate the penetration depth (e.g., P2 means Ponto guide drill with a penetration depth of 2.0 mm).



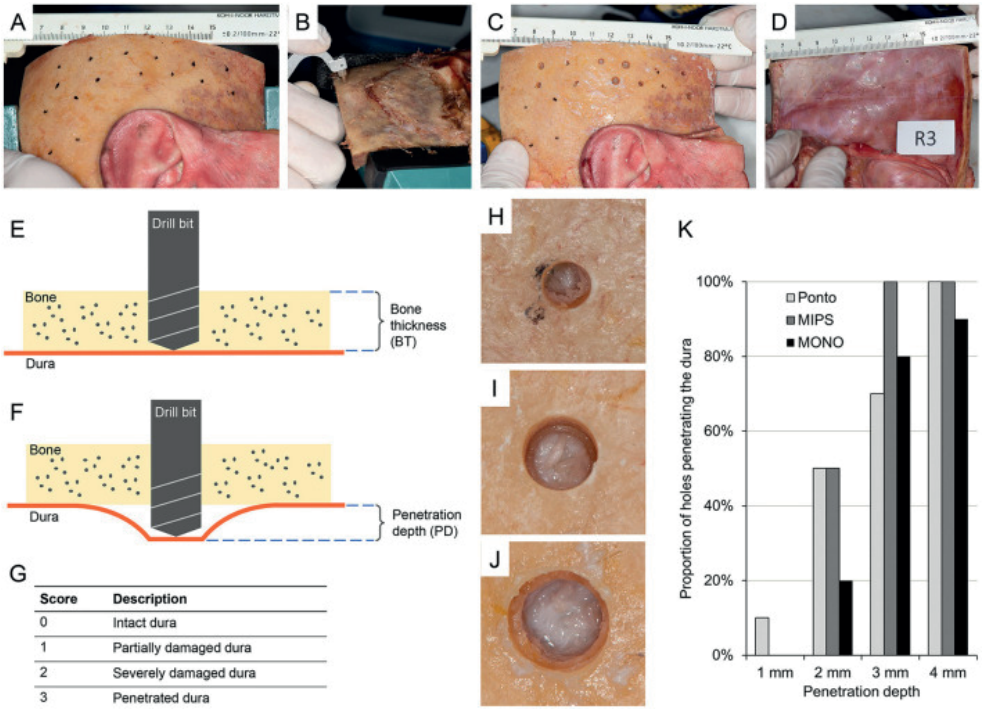
Test Procedure

The test procedure consisted of the following steps (Figures 3A–G):

- The temporal bone was identified, and soft tissue was removed.
- The drill sites were identified and marked according to the predetermined randomization scheme (Figure 2, Figure 3A), and the bone thickness (BT) at the sites was determined using a caliper (thickness gauge 2140–8105, domain 0–25 mm, accuracy 0.01 mm, Dasqua Tools, Cornegliano Laudense (LO), Italy) (Figures 3B,E). If a site could not be used for the stipulated test drill and test depth, the position was adjusted locally or moved to an alternative site on the bone.
- A drill site was selected, and a hole 0.5 mm shallower than the measured bone thickness was prepared using specially designed cannulas. The bottom of the hole was checked by visual inspection and palpation with a dissector. In the case of the presence of bone, a second cannula was used to drill deeper (with a maximum of 0.5 mm). When the dura was reached, this was defined as a "lower bone level" (Figure 3E).
- The drilling sequence against the dura was performed (Figures 3C,F). First, the drill was changed to a new one (i.e., a drill bit of the same type that is not used for hole preparation). Second, a new canula was used, which led to penetration depths of either 1.0, 2.0, 3.0 or 4.0 mm. As previously mentioned, the specific drill sites on the temporal bone were used to determine which penetration depth to use (according to the predetermined randomized schedule as outlined in Figure 2). Drilling was executed in a fast down-and-up motion while running the drill at 2 000 rpm using dental drill equipment (Drill unit SI-1023, Implantmed PLUS with hand piece WS-75 L, W&H Nordic AB, Täby, Sweden).
- The dura was inspected visually with a microscope (magnification x0.6 – x2.5, Zeiss OPMI Pico Surgical Microscope, Carl Zeiss AB, Stockholm, Sweden), and damage to the dura was scored according to a 4-point grading scale: 0 = intact dura, 1 = partially damaged dura, 2 = severely damaged dura and 3 = penetrated dura (Figures 3D,G). Four inspectors with expertise in the field of bone conduction devices (MLJ, AH, MT and JL) independently scored each hole. If at least one of the inspector's scores indicated penetration (a score of 3) for a specific hole, the dura was considered to be penetrated. If all investigators scored 2 or below, the dura was considered not to be penetrated.

The test facility was PO Medica AB (Sparsör, Sweden), and the dates of the experiment were 30 September and 1 October 2019.

Figure 3. (A) Temporal bone sample (item R3) with removed soft tissue and sites marked according to the randomization scheme. (B) The bone thickness (BT) at the sites determined using a caliper. (C) Photograph of a temporal bone sample (item R3) after drilling sequence. (D) Photograph of the dura of the same temporal bone sample (item R3) after drilling was performed. (E) Illustration of the preparation of holes in the temporal bone. (F) Illustration of penetration depth. The drill bit penetrates beyond the base of the skull bone to different depths. (G) Scoring scale of the impact of the drill on the dural tissue. (H) Example of a hole using the round burr (Ponto) with a score of 2 indicating severely damaged dura. (I) Example of a hole using a guide drill (MIPS) with a score of 1 indicating partially damaged dura. (J) Example of a hole using a MONO drill with a score of 0 indicating intact dura. (K) Proportion of holes penetrating the dura for the different drill systems (Ponto, MIPS, MONO) and penetration depths (1, 2, 3 and 4 mm). If at least one of the inspector's scores signified penetration (a score of 3) for a specific hole, the dura was considered penetrated. n = 10 holes for each drill system, and drill depth combination were prepared.



Results

A total of ten fresh frozen temporal bones from five patients were used in the test. For each penetration depth and each drill system, ten sites were prepared. Hence, a total of 120 holes were made with 12 holes in each temporal bone specimen. Examples of dural impact after a drilling sequence with the three different drill bits can be seen in Figures 3H–J. Fourteen drill sites (12%), which were mostly located in the supra-auricular area and not in the region on the temporal bone of the (clinical) BCD implantation site, could not be used. In all these cases, the holes were moved to an alternative site on the same bone to conform with the study protocol. There was an equal distribution in alternative sites for holes between the different drill systems and penetration depths.

The complete results from the tests are presented in Supplementary Material 1, with the derived median and mean scores of each site shown in Table 1. At a penetration depth of 1.0 mm, none of the drill bits caused penetration of the dura, except in one case (10%) when the guide drill in the LITT-P system (designated Ponto guide drill) was used (i.e., one of the ten holes) (Figure 3K). At a 2.0 mm penetration depth, half of the cases penetrated the dura when using the Ponto or MIPS guide drills, whereas the dura was penetrated in only two cases (20%) using the MONO drill (Figure 3K). When drilling deeper to 3.0 and 4.0 mm beyond the inner bone level, 70% or more of the drill sequences caused penetration of the dura irrespective of the system (Figure 3K). The median and mean scores are in line with this trend. A sensitivity analysis with the cut-off threshold for dural penetration set to 2 points (i.e., the dura was considered penetrated if at least one inspector scored 2 or above) demonstrated a similar trend.

Table 1. The mean (± standard deviation) and median scores for damage to the dura with different drilling systems and penetration depths. The dura scoring systems were graded as follows: 0, intact dura; 1, partially damaged dura; 2, severely damaged dura and 3, penetrated dura. The abbreviations used for the drilling systems are P, Ponto guide drill; M, MIPS guide drill and MO, MONO drill. The numbers behind the drilling systems indicate the penetration depth (e.g., P2 means Ponto guide drill with a penetration depth of 2.0 mm).

	Mean score (± SD)	Median score
P1	1.20 (0.69)	1
P2	2.25 (0.78)	2
P3	2.28 (1.01)	3
P4	2.70 (0.56)	3
M1	1.10 (0.67)	1
M2	2.25 (0.78)	2
M3	2.70 (0.61)	3
M4	2.68 (0.69)	3
MO1	1.08 (0.61)	1
MO2	1.63 (0.87)	2
MO3	2.70 (0.52)	3
MO4	2.73 (0.55)	3

Discussion

MIPS represents a promising minimally invasive, punch-only, surgical technique for BCD implantation. Comparable or improved soft tissue outcomes in combination with better results registered in surgical time, cosmetics, skin sensibility and in the field of cost analysis compared with the outcomes of traditional techniques can corroborate this statement.[25-29,32,33,37] These encouraging features make this technique relevant to improve and to further streamline the procedure to install a BCD. A new one-stage drilling procedure, called the MONO procedure (Oticon Medical), has been developed.[39,40] With this MONO drilling system, the final osteotomy site for a 4 mm implant is created in a single drill stage, in contrast to the available systems that employ a three-step drill sequence. It is possible that the reduced total drilling time and reduced heat generation may lead to less negative effects on the peri-implant bone and osseointegration.[39,40] Moreover, since some studies have reported lower implant survival with MIPS compared with LITT-P[25,26,34], developments leading to improved implant survival and stability outcomes using minimally invasive approaches are warranted.

In this ex vivo experimental study of human temporal bone samples, the novel MONO drill bit was compared with the guide drills of the LITT-P and MIPS systems in terms of damage and possible penetration of the dura. Interestingly, the MONO drill bit was less prone to inflict damage to the dura than the LITT-P and MIPS systems. Moreover, the MONO drill resulted in less penetration of the dura than the guide drills when the drill depth exceeded the mastoid bone thickness by 2 mm. A possible explanation for these findings could be related to the differences in the design of the drill bit tips. The tip diameters of the round burr in the LITT-P system and the MIPS guide drill are 2.3 and 2.4 mm, respectively. In contrast, the diameter of the MONO drill is 3.8 mm, resulting in a larger area of contact between the rotating drill tip and the dura tissue. In addition, the detailed design of the cutting edges differs between the three drill types. Another finding of the study was the fact that the dura is likely to be penetrated when the drill depth exceeds the mastoid bone thickness of more than 2 mm, irrespective of the drill system used. In a clinical situation, this would correspond to a mastoid bone thickness of <3.0 mm, 2.9 mm and 2.75 mm when using the LITT-P, MIPS and MONO systems, respectively.

Using the MONO procedure, the full depth (4.75 mm) of the osteotomy site was reached in a single drilling sequence, in contrast to the currently available systems where the drilling sequence is halted 1 mm before the full depth is reached to permit verification of bone tissue in the bottom of the osteotomy site before proceeding with the second drill step. Therefore, the impact of exposed dura during the drilling sequence may become more relevant. As stated in the introduction, previous research showed that 95% of adults have a bone thickness of 5 mm or more in the region of BCD implantation.[42] This means that the MONO procedure should be considered a safe option for adult patients. However, the chance of encountering the dura is potentially more likely with this procedure than when using conventional systems. A recent systematic review showed that the mastoid bone is penetrated in ~6% of BCD surgeries.[8] Obviously, a higher proportion could be expected in the pediatric population.[43] There is, however, no indication that exposure of the dura would increase the complication rates in these patients. The penetration of the mastoid bone followed by penetration of the dura, with a resulting cerebrospinal fluid leak, is reported in the literature with a frequency of 0.3% of the cases, although without any serious adverse events reported in conjunction with this.[8]

This experimental study has several strengths, some of which were present because the current test procedure was based on the fundaments and learning of two previous pilot studies. First, the localization on the temporal bone sample for the different test drills and test depths was randomly assigned. This led to a randomized predetermined scheme, which reduced possible effects on the results due to dissimilarity in temporal bone samples and position. Second, the temporal bones and dura of the samples were of good quality. This applied to all measurements because in case a site could not be used for the stipulated test drill and test depth according to scheme, e.g., because of insufficient quality of bone and/or dura, the position was adjusted locally or an alternative site on the bone was chosen. Third, an asset of the study was the ability to reach the level of the dura (i.e., lower bone level) precisely. This was accomplished by using a caliper to accurately identify the bone thickness before drilling. Additionally, this successful control of the drill depth was warranted by the implementation of step (iii) in the test procedure. This step consisted of preparing a hole using a cannula with a length of <0.5 mm compared to the measured bone thickness. This could be further deepened stepwise (in case the dura was not reached) using a second cannula with steps of <0.5 mm. A fourth strong facet of the experiment was the change to a new drill bit before drilling against the dura. This change prevented possible influences of instrumental wear on the drill bit. Another strength that should be considered was adequate documentation and photos of the temporal bone samples (Nikon D805 with AF-S Micro Nikkor 105 mm 2.8G ED). These are important factors for a clear and reproducible experimental study. Finally, grading was performed by professionals in the field of BCDs who scored the different drilled holes independently.

Nevertheless, some limitations of the study should be noted. First, the grading by observers was not fully blinded. Two of the four inspectors (MLJ and AH) performed both drilling and grading. Additionally, there was some considerable interobserver variability using our grading classification. Perhaps a more standardized approach/instruction for the inspectors could be useful. Another consideration may be the use of only one operator because subtle differences in drilling cannot be eliminated. Inevitable, interesting points were noted in the difference between “in vivo” tissue and cadaveric human temporal bone. However, these fresh frozen samples resemble “in vivo” outcomes better than artificial dura. Finally, it is important to recognize that in a clinical situation other side effects resulting from the drilling sequence may occur, e.g., bleeding from the bone and/or dura is commonly observed.

In conclusion, the novel MONO drilling procedure is not more inclined to penetrate the dura in cadaveric temporal human bone compared with drills used for the LITT-P and MIPS procedures. Based on the possible advantages of a one-step procedure for creating the osteotomy site, the MONO drilling procedure should be further developed, and its clinical useability should be evaluated.

Acknowledgement

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Supplementary Material

Supplementary Material 1: Overview of the scoring of dura damage at the different drilling sites with different drilling systems and penetration depths.

The bone sample (1- 5 with left (L) and right (R)), different drill operators (MLJ and AH) and inspectors (MLJ, AH, MT and JL) are indicated. Used abbreviations for the drilling systems are P = Ponto guide drill (linear incision), M= MIPS guide drill and MO = MONO drill. The numbers behind the drilling systems indicate the penetration depth (e.g., P2 means Ponto guide drill with penetration depth 2.0 mm). Y/N indicates whether the dura was penetrated or not. If at least one investigator scored 3 (penetration) it was scored penetrated (=Y).

Bone ID	L1					R1				
Drill operator	MLJ					AH				
Investigator	MLJ	AH	MT	JL	**Penetrated? Y/N**	MLJ	AH	MT	JL	**Penetrated? Y/N**
P1	1	3	1	2	**Y**	2	1	1	1	**N**
P2	3	3	3	2	**Y**	2	2	1	2	**N**
P3	3	3	3	3	**Y**	2	1	1	2	**N**
P4	3	3	3	3	**Y**	3	3	3	3	**Y**
M1	2	2	2	0	**N**	2	1	1	0	**N**
M2	2	2	1	1	**N**	3	3	3	3	**Y**
M3	3	2	3	2	**Y**	3	3	3	3	**Y**
M4	3	3	3	3	**Y**	1	3	0	2	**Y**
MO1	2	1	1	0	**N**	2	1	1	0	**N**
MO2	1	2	2	0	**N**	2	2	1	2	**N**
MO3	3	3	3	3	**Y**	3	3	3	3	**Y**
MO4	1	2	1	2	**N**	3	3	3	3	**Y**

Bone ID	L2					R2				
Drill operator	AH					MLJ				
Investigator	MLJ	AH	MT	JL	**Penetrated? Y/N**	MLJ	AH	MT	JL	**Penetrated? Y/N**
P1	1	1	0	0	**N**	2	2	2	2	**N**
P2	3	2	3	3	**Y**	2	2	1	2	**N**
P3	2	2	0	1	**N**	3	3	3	3	**Y**
P4	3	2	3	2	**Y**	3	2	3	2	**Y**
M1	1	1	0	1	**N**	1	2	1	1	**N**
M2	3	3	3	3	**Y**	3	3	3	3	**Y**
M3	3	3	3	3	**Y**	3	3	3	3	**Y**
M4	3	2	3	3	**Y**	3	3	3	3	**Y**

Bone ID	L2					R2				
Drill operator	AH					MLJ				
Investigator	MLJ	AH	MT	JL	**Penetrated? Y/N**	MLJ	AH	MT	JL	**Penetrated? Y/N**
MO1	2	1	1	0	**N**	1	1	2	1	**N**
MO2	2	2	0	1	**N**	3	2	3	3	**Y**
MO3	3	3	3	3	**Y**	3	3	3	3	**Y**
MO4	3	3	3	2	**Y**	3	3	3	3	**Y**

Bone ID	L3					R3				
Drill operator	MLJ					AH				
Investigator	MLJ	AH	MT	JL	**Penetrated? Y/N**	MLJ	AH	MT	JL	**Penetrated? Y/N**
P1	1	2	1	0	**N**	1	0	0	1	**N**
P2	3	3	3	3	**Y**	3	3	3	3	**Y**
P3	3	3	3	3	**Y**	1	2	3	2	**Y**
P4	2	2	3	2	**Y**	3	3	1	3	**Y**
M1	0	0	1	1	**N**	1	1	0	2	**N**
M2	2	2	1	1	**N**	1	2	1	2	**N**
M3	2	1	3	1	**Y**	1	2	3	3	**Y**
M4	3	2	3	2	**Y**	3	3	3	3	**Y**
MO1	1	0	1	1	**N**	1	1	1	0	**N**
MO2	1	1	1	1	**N**	1	2	2	1	**N**
MO3	3	3	3	3	**Y**	2	2	3	2	**Y**
MO4	2	2	3	3	**Y**	2	2	3	3	**Y**

Bone ID	L4					R4				
Drill operator	AH					MLJ				
Investigator	MLJ	AH	MT	JL	**Penetrated? Y/N**	MLJ	AH	MT	JL	**Penetrated? Y/N**
P1	1	1	2	1	**N**	1	1	2	1	**N**
P2	3	3	3	3	**Y**	1	2	2	2	**N**
P3	3	3	3	3	**Y**	3	3	3	3	**Y**
P4	1	3	3	3	**Y**	3	3	3	3	**Y**
M1	1	0	1	1	**N**	2	2	2	1	**N**
M2	2	2	2	2	**N**	2	3	3	3	**Y**
M3	3	3	3	3	**Y**	3	3	3	3	**Y**

Bone ID	L4					R4				
Drill operator	AH					MLJ				
Investigator	MLJ	AH	MT	JL	**Penetrated? Y/N**	MLJ	AH	MT	JL	**Penetrated? Y/N**
M4	3	3	3	3	**Y**	3	3	3	3	**Y**
MO1	2	1	1	1	**N**	2	2	2	1	**N**
MO2	1	2	2	2	**N**	3	3	3	3	**Y**
MO3	1	2	2	2	**N**	3	3	3	3	**Y**
MO4	3	3	3	3	**Y**	3	3	3	3	**Y**

Bone ID	L5					R5				
Drill operator	MLJ					AH				
Investigator	MLJ	AH	MT	JL	**Penetrated? Y/N**	MLJ	AH	MT	JL	**Penetrated? Y/N**
P1	1	1	2	1	**N**	1	2	1	1	**N**
P2	1	1	2	1	**N**	1	1	2	2	**N**
P3	1	3	3	3	**Y**	1	0	1	0	**N**
P4	3	3	3	3	**Y**	3	3	3	2	**Y**
M1	2	1	1	1	**N**	1	2	1	1	**N**
M2	3	3	3	2	**Y**	2	2	1	1	**N**
M3	3	3	3	3	**Y**	2	3	3	2	**Y**
M4	1	2	3	2	**Y**	3	3	3	3	**Y**
MO1	2	1	1	0	**N**	1	1	1	1	**N**
MO2	1	1	2	1	**N**	1	1	1	0	**N**
MO3	3	3	3	3	**Y**	2	2	2	2	**N**
MO4	3	3	3	3	**Y**	3	3	3	3	**Y**

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7

HEALTH ECONOMIC COST ANALYSIS FOR PERCUTANEOUS BONE CONDUCTION DEVICES: THE MINIMALLY INVASIVE PONTO SURGERY VERSUS LINEAR INCISION TECHNIQUE WITH TISSUE PRESERVATION

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Submitted.

Abstract

Objectives: To identify differences in mean cost per patient between the Minimally Invasive Ponto Surgery (MIPS) and Linear Incision Technique with Tissue Preservation (LITT-P).

Study design: Health economic cost analysis.

Setting: The analysis was performed in a randomized multicenter controlled trial cohort.

Patients: Adult patients eligible for unilateral bone conduction devices surgery.

Interventions: MIPS versus LITT-P surgery for BCD implantation.

Main outcome measures: Peroperative and post-operative costs were identified and compared.

Results: The difference in mean cost per patient between both techniques is € 77.83 in favour of the MIPS after complete of follow-up. The mean costs per patient were lower in the MIPS cohort for surgery (€ 145.68), outpatient visits (€ 24.27), systemic antibiotic therapy with amoxicillin/clavulanic acid (€ 0.30) or clindamycin (€ 0.40), abutment change (€ 0.36) and abutment removal (€ 0.18). The mean costs per patient were higher for implant and abutment set (€ 18.00), topical treatment with hydrocortison/oxytetracycline/polymyxine B (€ 0.43), systemic therapy with azithromycin (€ 0.09) or erythromycin (€ 1.15), local revision surgery (€ 1.45), elective explantation (€ 1.82) and implant extrusion (€ 70.42). The analysis of scenarios in case all patients were operated under general or local anaesthesia and with mutation of implant loss to current situation showed that differences in mean cost per patient were also in favour of the MIPS.

Conclusion: The difference between the MIPS and LITT-P in mean cost per patient is € 77.83 in favour of the MIPS after long-term follow-up. The MIPS is an economically responsible technique and could be promising for the future.

Introduction

The World Health Organization estimates that around 466 million people have disabling hearing loss.[1] Hearing loss has a significantly functional, emotional and social impact[1] and is associated with enormous socio-economic costs.[2] This highlights the relevance of hearing rehabilitation with hearing aids like bone conduction devices (BCDs). The principle of bone conduction hearing was the fundament for the development of these osseointegrated BCDs.[3] Nowadays, BCDs have proved to be an important option for patients with uni- and bilateral conductive or mixed hearing loss[3-5] and patients with single-sided deafness[6].

The field of BCDs is characterized by ongoing developments in implant and abutment design as well as the surgical technique. Since the first implantation by Tjellström in 1977[3], the surgical procedure is improved in efficiency with decreased invasiveness, including the introduction of the free retro-auricular full-thickness skin graft, pedicled grafts, dermatome technique and linear incision technique.[7,8] The latter procedure was initially performed with tissue reduction.[9] Nowadays, the less invasive linear incision technique with tissue preservation is advocated, causing similar or less (adverse) soft tissue reactions[10-16] as well as favourable outcomes in surgical time, cosmetics and numbness[15-21]. Recently, minimally invasive punch-only techniques are introduced in order to reduce soft tissue trauma.[22-34] A standardized approach was developed by Oticon Medical AB (Askim, Sweden): the Minimally Invasive Ponto Surgery (MIPS).[26]

The first short-term results of a multicentre evaluation of the MIPS technique were promising, with a short surgical time in combination with minimal intra-operative complications (i.e. only one case of cerebrospinal fluid leak) and soft tissue reactions (5% adverse soft tissue reactions registered in 160 visits) as well as an implant survival rate >95% at 20 weeks follow-up.[27] Subsequent studies comparing the MIPS technique to the LITT-P showed similarly favourable outcomes, even with longer follow-up, regarding soft tissue reactions.[28-34] In these studies a significantly shorter surgical time for the MIPS was reported.[28-34] Some studies were reporting better cosmetic appearance[29,30] and improved sensibility[29] in the MIPS cohort in comparison with the LITT-P group. However, implant loss was mentioned as a concern after the MIPS procedure with a couple of studies showing (non-significantly) more implant extrusion.[29,30] Recently, Strijbos et al. published long-term (22-months) follow-up results,

which demonstrated no differences regarding soft tissue reactions, pain, patient satisfaction and quality of life.[34]

Apart from these favourable outcomes in quality, safety and surgical results of the MIPS [27-34], from societal perspective, it is also important to take the resources and costs into account when introducing an (alternative) surgical technique. A health economic study can be used to improve understanding of benefits, harms and costs of interventions and contribute to informed decision making. To our knowledge, there are no previous well-designed health economic studies evaluating differences in costs between these different surgical techniques for implantation of BCDs. One study performed a direct cost comparison between the MIPS and open approaches, showing the MIPS technique more cost effective than the previous procedures.[35] Nonetheless, the retrospective study design, small patient population (n = 12), remarkably great difference in surgical time (MIPS on average more than hour shorter) and the lack of including postoperative costs are limitations of this study. Moreover, the MIPS procedure was not carried out in an operation room in contrast to the open approach leading to obvious economic benefits.[35]

The aim of the current study is to perform a health cost analysis to identify differences in mean cost per patient between the MIPS and LITT-P technique in our randomized controlled trial cohort[36] of adult patients eligible for unilateral BCD surgery during a long-term 22 months follow-up.

Materials and Methods

Study design and participants

This health economic study is part of a multicentre randomized controlled trial in the Netherlands (Maastricht University Medical Centre, Ziekenhuisgroep Twente and Medisch Centrum Leeuwarden). The protocol of this study was published previously[36], as well as the surgical outcomes after three months[29] and 22 months follow-up[34].

Adult patients (≥18 years) with the eligibility of unilateral BCD surgery were included. Patients were excluded if there was a history of immunosuppressive medication and/or immunosuppressive systemic disease, relevant dermatological disease, bilateral placement

of BCDs and participation in other studies. In case of peroperative absence of a suitable implantation site for a 4.0-mm implant or insufficient bone quality, the subject was regarded as early termination and excluded from the study. All enrolled subjects were randomized in each research centre independently in a 1:1 ratio stratified for gender. The test group was the MIPS technique and the control cohort was the LITT-P.

Type of health economic evaluation

In this randomized controlled trial, the quality of life was assessed by the Health Utilities Index Mark III (HUI-III), Abbreviated Profile of Hearing Aid Benefit (APHAB) and ICEpop CAPability measure for Adults (ICECAP-A). As previously published, there was no difference in overall quality of life between the MIPS and LITT-P after complete follow-up.[34] Therefore quality of life was not included in this economic evaluation and only a cost analysis was performed.

Besides the main analysis, there were three additional analyses performed based on clinical scenarios. The first scenario was simulating the situation if all patients in both groups underwent their surgery under general anesthesia. The second scenario was simulating this situation for local anesthesia. The reason for this is that the choice of anesthesia was only based on patient's preferences and independent of the surgical technique. The last scenario was simulating the situation if most recent data for implant loss with the modified MIPS technique were applied, because a trend towards less implant extrusion was observed with implementation of a modified MIPS drill system.[37]

The costs were subdivided in two categories: peroperative and postoperative costs. Both were evaluated during complete 22 month follow-up. The total costs and mean cost per patient were calculated for all aspects for both techniques. The difference in total costs and mean cost per patient between the MIPS and LITT-P could be derived from this. Also, the cumulative (difference in) total and mean costs per patient could be extracted. The costs were displayed in euros (€).

Cost identification

The peroperative costs consisted first of all of the surgery itself. This was registered as the surgical time, i.e. the duration from start incision until the end of the surgical procedure. The

costs were defined as the cost of a fully equipped operation room, including staff per minute. The difference between costs of local and general anesthesia was the fee of the anesthesiologist (only necessary in case of general anesthesia). These costs were obtained from the University Medical Centre Utrecht. Furthermore, the implant and abutment set are part of the peroperative costs. The total prices were censored because of their confidential background. However, Oticon Medical AB provided the difference in costs between the MIPS and LITT-P, which was € 18.00 in favour of the LITT-P set. Finally, patients were admitted to the surgical ward for one day after both techniques (daycare). The cost of admission was based on mean reference prices for Dutch hospitals from the Dutch National Healthcare Institute (Zorginstituut Nederland).[38]

The post-operative costs were subdivided in outpatient visits and treatment of possible complications. The total of outpatient visits was the sum of the regular post-operative visits including all extra BCD-related outpatient visits in case of complications or problems. The price of an outpatient visit was based on mean reference prices for Dutch hospitals from the Dutch National Healthcare Institute.[38] Possible and number of complications, including all adverse events, were identified by reviewing all filled-out clinical research forms. This resulted in identification of the items topical therapy (hydrocortison/oxytetracycline/polymyxine B), systemic antibiotics (amoxicillin/clavulanic acid, azitromycin, clindamycin, erythromycin), abutment change or removal, local skin revision surgery for skin overgrowth, elective explantation and implant extrusion.

The duration of topical or systemic therapy was derived from the clinical research forms. In case the end date of the therapy was not described, a standard cure for that specific medicine was assumed. The costs were obtained from the Dutch national Pharmacotherapeutical Guide.[39] Prices of generic medicines were applied in the analysis. The costs for abutment change or removal, local revision surgery and elective explantation were estimated based on the mean costs of these procedures last three years as registered by the Cost Administration of the University Medical Centre Utrecht. Finally, the cost of an extruded implant was defined as the mean cost per patient for all peroperative costs for that technique. Nota bene: this was independent of a patient's choice of actual implant replacement after an event of extrusion.

Ethics

This study was performed in accordance with ISO 14155:2011 and the Declaration of Helsinki. There was approval by the ethics committee at Maastricht University Medical Centre+ (NL500720.068.14), Medisch Centrum Leeuwarden and Ziekenhuisgroep Twente. Also, there was registration in ClinicalTrials.gov NCT02438618. The participation of subjects was voluntary and all subjects provided written informed consent. The investigators had full access to all data. Monitoring was performed independently. The study was sponsored by Oticon Medical AB (Askim, Sweden).

Results

Baseline characteristics

A total of 64 participants were included between December 2014 and August 2016. Thirty-three subjects were randomized to the test cohort (52%) and 31 to the control cohort (48%). One patient was excluded from the analyses due to placement of a 3-mm implant. This resulted in 63 subjects being analysed with 33 in the MIPS and 30 in the LITT-P group. Baseline characteristics were comparable between the groups (more extensive baseline information was published in an earlier paper[29,34]). The surgery was performed under local anaesthesia in n = 17 (52%) and n = 13 (43 %) of the cases for the MIPS and LITT-P groups, respectively.

Cost analysis

The difference in mean cost per patient between both technique is € 77.83 in favour of the MIPS after 22 months of follow-up (Table 1). The mean costs per patients were in favour of the MIPS for surgery (€ 145.68), outpatient visits (€ 24.27), systemic antibiotic therapy with amoxicillin/clavulanic acid (€ 0.30) or clindamycin (€ 0.40), abutment change (€ 0.36) and abutment removal (€ 0.18). The mean costs per patient were in favour of the LITT-P cohort for implant and abutment set (€ 18.00), topical treatment with hydrocortison/oxytetracycline/polymyxine B (€ 0.43), systemic therapy with azithromycin (€ 0.09) or erythromycin (€ 1.15), local revision surgery (€ 1.45), elective explantation (€ 1.82) and implant extrusion (€ 70.42). There were no differences in mean costs per patient in admission to the patient ward between both cohorts.

Table 1. The costs in peroperative and postoperative course of the MIPS and LITT-P including the difference between the procedures after 22 months follow-up. The costs are displayed in euros (€).

* The 'costs per unit' for surgery are indicated per minute.

** The difference in price of local anesthesia is the fee of the anesthesiologist.

*** Outpatient visits cover all regular visits and extra consultations for BCD related issues.

**** These costs are exclusive abutment price.

	MIPS						**LITT-P**						**Differences MIPS versus LITT-P**	
	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total costs	Mean costs/ patient
PEROPERATIVE														
Surgery*														
Local anesthesia**	17	0.52	20.67	7.29	2561.63	77.63	13	0.43	20.67	13.69	3678.64	122.62	-1117.01	-45.00
General anesthesia	16	0.48	21.85	5.69	1989.22	60.28	17	0.57	21.85	13.00	4828.85	160.96	-2839.63	-100.68
Implant & Abutment (per set)	33	1.00	X +18	n/a	33 · (X +18.00)	X + 18.00	30	1.00	X	n/a	30 · X	X	n/a	18.00
Admission patient ward (days)	33	1.00	476.00	n/a	15708.00	476.00	30	1.00	476.00	n/a	14280.00	476.00	1428.00	0.00
POSTOPERATIVE														
Outpatient visits***	187	5.67	91.00	n/a	17017.00	515.67	178	5.93	91.00	n/a	16198.00	539.93	819.00	-24.27
Treatment complications														
- Topical treatment (per cure)														

	MIPS						LITT-P						Differences MIPS versus LITT-P	
	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total costs	Mean costs/ patient
Hydrocortison/ oxytetracycline/ polymyxine B - Systemic antibiotics (per cure)	81	2.45	2.76	n/a	223.56	6.77	69	2.30	2.76	n/a	190.44	6.35	33.12	0.43
Amoxicillin/ clavulanic Acid	4	0.12	2.66	n/a	10.64	0.32	7	0.23	2.66	n/a	18.62	0.62	-7.98	-0.30
Azithromycin	2	0.06	3.15	n/a	6.30	0.19	1	0.03	3.15	n/a	3.15	0.11	3.15	0.09
Clindamycin	1	0.03	10.99	n/a	10.99	0.33	2	0.07	10.99	n/a	21.98	0.73	-10.99	-0.40
Erythromycin	4	0.12	9.45	n/a	37.80	1.15	0	0.00	9.45	n/a	0.00	0.00	37.80	1.15
- Abutment change****	2	0.06	60.00	n/a	120.00	3.64	2	0.06	60.00	n/a	120.00	4.00	0.00	-0.36
- Abutment removal****	1	0.03	60.00	n/a	60.00	1.82	1	0.03	60.00	n/a	60.00	2.00	0.00	-0.18
- Local revision surgery	3	0.09	60.00	n/a	180.00	5.45	2	0.06	60.00	n/a	120.00	4.00	60.00	1.45
- Elective explantation	1	0.03	60.00	n/a	60.00	1.82	0	0.00	60.00	n/a	0.00	0.00	60.00	1.82
- Implant extrusion	5	0.15	631.90	n/a	3159.52	95.74	1	0.03	759.58	n/a	759.58	25.32	2399.94	70.42
CUMULATIVE					41738.67	1264.81					40279.26	1342.64	865.41	-77.83

Additional scenarios cost analysis

The first scenario explored the simulated clinical situation in case all patients in both cohorts had surgery under general anesthesia, which led to a difference in mean cost per patient between both techniques of € 93.95 in favour of the MIPS after 22 months of follow-up (Table 2). The second scenario elaborated the simulated clinical situation in case all patients in both cohorts had surgery under local anesthesia. This scenario showed a € 62.49 difference in mean cost per patient between both techniques in favour of the MIPS after complete follow-up (Table 3). In the final scenario, the more realistic implant loss of 4.0% for the MIPS was used, based on the latest study using the modified drill system[40]. The difference in mean cost per patient was increased to € 154.43 in favour of the MIPS (Table 4).

Table 2. The costs in peroperative and postoperative course of the MIPS and LITT-P including the difference between the procedures after 22 months follow-up for the scenario if all patients were operated under general anesthesia. The costs are displayed in euros (€).

* The 'costs per unit' for surgery are indicated per minute.

** Outpatient visits cover all regular visits and extra consultations for BCD related issues.

*** These costs are exclusive abutment price.

	MIPS						**LITT-P**						**Differences MIPS versus LITT-P**	
	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total costs	Mean costs/ patient
PEROPERATIVE														
Surgery*														
General anesthesia	33	1.00	21.85	5.69	4102.77	124.33	30	1.00	21.85	13.00	8521.50	284.05	-4418.73	-159.72
Implant & Abutment (per set)	33	1.00	X +18	n/a	33 · (X +18.00)	X + 18.00	30	1.00	X	n/a	30 · X	X	n/a	18.00
Admission patient ward (days)	33	1.00	476.00	n/a	15708.00	476.00	30	1.00	476.00	n/a	14280.00	476.00	1428.00	0.00
POSTOPERATIVE														
Outpatient visits**	187	5.67	91.00	n/a	17017.00	515.67	178	5.93	91.00	n/a	16198.00	539.93	819.00	-24.27
Treatment complications														
- Topical treatment (per cure)														

	MIPS						LITT-P						Differences MIPS versus LITT-P	
	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total costs	Mean costs/ patient
Hydrocortison/ oxytetracycline/ polymyxine B	81	2.45	2.76	n/a	223.56	6.77	69	2.30	2.76	n/a	190.44	6.35	33.12	0.43
- Systemic antibiotics (per cure)														
Amoxicillin/ clavulanic acid	4	0.12	2.66	n/a	10.64	0.32	7	0.23	2.66	n/a	18.62	0.62	-7.98	-0.30
Azithromycin	2	0.06	3.15	n/a	6.30	0.19	1	0.03	3.15	n/a	3.15	0.11	3.15	0.09
Clindamycin	1	0.03	10.99	n/a	10.99	0.33	2	0.07	10.99	n/a	21.98	0.73	-10.99	-0.40
Erythromycin	4	0.12	9.45	n/a	37.80	1.15	0	0.00	9.45	n/a	0.00	0.00	37.80	1.15
- Abutment change***	2	0.06	60.00	n/a	120.00	3.64	2	0.06	60.00	n/a	120.00	4.00	0.00	-0.36
- Abutment removal***	1	0.03	60.00	n/a	60.00	1.82	1	0.03	60.00	n/a	60.00	2.00	0.00	-0.18
- Local revision surgery	3	0.09	60.00	n/a	180.00	5.45	2	0.06	60.00	n/a	120.00	4.00	60.00	1.45
- Elective explantation	1	0.03	60.00	n/a	60.00	1.82	0	0.00	60.00	n/a	0.00	0.00	60.00	1.82
- Implant extrusion	5	0.15	618.33	n/a	3091.63	93.69	1	0.03	760.05	n/a	760.05	25.34	2331.58	68.35
CUMULATIVE					41222.70	1249.17					40293.74	1343.12	334.96	-93.95

Table 3. The costs in peroperative and postoperative course of the MIPS and LITT-P including the difference between the procedures after 22 months follow-up for the scenario if all patients were operated under local anesthesia. The costs are displayed in euros (€).

* The 'costs per unit' for surgery are indicated per minute.

** Outpatient visits cover all regular visits and extra consultations for BCD related issues.

*** These costs are exclusive abutment price.

	MIPS						**LITT-P**						**Differences MIPS versus LITT-P**	
	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total costs	Mean costs/ patient
PEROPERATIVE														
Surgery*														
Local anesthesia	33	1.00	20.67	7.29	4972.58	150.68	30	1.00	20.67	13.69	8489.17	282.97	-3516.59	-132.29
Implant & Abutment (per set)	33	1.00	X +18	n/a	33 · (X +18.00)	X + 18.00	30	1.00	X	n/a	30 · X	X	n/a	18.00
Admission patient ward (days)	33	1.00	476.00	n/a	15708.00	476.00	30	1.00	476.00	n/a	14280.00	476.00	1428.00	0.00
POSTOPERATIVE														
Outpatient visits**	187	5.67	91.00	n/a	17017.00	515.67	178	5.93	91.00	n/a	16198.00	539.93	819.00	-24.27
Treatment complications														
- Topical treatment (per cure)														

	MIPS						LITT-P						Differences MIPS versus LITT-P	
	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total costs	Mean costs/ patient
Hydrocortison/ oxytetracycline/ polymyxine B - Systemic antibiotics (per cure)	81	2.45	2.76	n/a	223.56	6.77	69	2.30	2.76	n/a	190.44	6.35	33.12	0.43
Amoxicillin/ clavulanic acid	4	0.12	2.66	n/a	10.64	0.32	7	0.23	2.66	n/a	18.62	0.62	-7.98	-0.30
Azithromycin	2	0.06	3.15	n/a	6.30	0.19	1	0.03	3.15	n/a	3.15	0.11	3.15	0.09
Clindamycin	1	0.03	10.99	n/a	10.99	0.33	2	0.07	10.99	n/a	21.98	0.73	-10.99	-0.40
Erythromycin	4	0.12	9.45	n/a	37.80	1.15	0	0.00	9.45	n/a	0.00	0.00	37.80	1.15
- Abutment change***	2	0.06	60.00	n/a	120.00	3.64	2	0.06	60.00	n/a	120.00	4.00	0.00	-0.36
- Abutment removal***	1	0.03	60.00	n/a	60.00	1.82	1	0.03	60.00	n/a	60.00	2.00	0.00	-0.18
- Local revision surgery	3	0.09	60.00	n/a	180.00	5.45	2	0.06	60.00	n/a	120.00	4.00	60.00	1.45
- Elective explantation	1	0.03	60.00	n/a	60.00	1.82	0	0.00	60.00	n/a	0.00	0.00	60.00	1.82
- Implant extrusion	5	0.15	644.68	n/a	3223.42	97.68	1	0.03	758.97	n/a	758.97	25.30	2464.45	72.38
CUMULATIVE					42224.29	1279.52					40260.33	1342.01	1369.96	-62.49

Table 4. The costs in peroperative and postoperative course of the MIPS and LITT-P including the difference between the procedures after 22 months follow-up for the scenario with modified extrusion rate to current clinical practice . The costs are displayed in euros (€).

* The 'costs per unit' for surgery are indicated per minute.

** The difference in price of local anesthesia is the fee of the anesthesiologist.

*** Outpatient visits cover all regular visits and extra consultations for BCD related issues.

**** These costs are exclusive abutment price.

	MIPS						**LITT-P**					**Differences MIPS versus LITT-P**		
	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total events	Events per patient	Costs (€) per unit	Mean time	Total costs	Mean costs/ patient	Total costs	Mean costs/ patient
PEROPERATIVE														
Surgery*														
Local anesthesia**	17	0.52	20.67	7.29	2561.63	77.63	13	0.43	20.67	13.69	3678.64	122.62	-1117.01	-45.00
General anesthesia	16	0.48	21.85	5.69	1989.22	60.28	17	0.57	21.85	13.00	4828.85	160.96	-2839.63	-100.68
Implant & Abutment (per set)	33	1.00	X +18	n/a	33 · (X +18.00)	X + 18.00	30	1.00	X	n/a	30 · X	X	n/a	18.00
Admission patient ward (days)	33	1.00	476.00	n/a	15708.00	476.00	30	1.00	476.00	n/a	14280.00	476.00	1428.00	0.00
POSTOPERATIVE														
Outpatient visits***	187	5.67	91.00	n/a	17017.00	515.67	178	5.93	91.00	n/a	16198.00	539.93	819.00	-24.27
Treatment complications														

	MIPS						LITT-P					Differences MIPS versus LITT-P		
- Topical treatment (per cure)														
Hydrocortison/ oxytetracycline/ polymyxine B	81	2.45	2.76	n/a	223.56	6.77	69	2.30	2.76	n/a	190.44	6.35	33.12	0.43
- Systemic antibiotics (per cure)														
Amoxicillin/ clavulanic acid	4	0.12	2.66	n/a	10.64	0.32	7	0.23	2.66	n/a	18.62	0.62	-7.98	-0.30
Azithromycin	2	0.06	3.15	n/a	6.30	0.19	1	0.03	3.15	n/a	3.15	0.11	3.15	0.09
Clindamycin	1	0.03	10.99	n/a	10.99	0.33	2	0.07	10.99	n/a	21.98	0.73	-10.99	-0.40
Erythromycin	4	0.12	9.45	n/a	37.80	1.15	0	0.00	9.45	n/a	0.00	0.00	37.80	1.15
- Abutment change****	2	0.06	60.00	n/a	120.00	3.64	2	0.06	60.00	n/a	120.00	4.00	0.00	-0.36
- Abutment removal****	1	0.03	60.00	n/a	60.00	1.82	1	0.03	60.00	n/a	60.00	2.00	0.00	-0.18
- Local revision surgery	3	0.09	60.00	n/a	180.00	5.45	2	0.06	60.00	n/a	120.00	4.00	60.00	1.45
- Elective explantation	1	0.03	60.00	n/a	60.00	1.82	0	0.00	60.00	n/a	0.00	0.00	60.00	1.82
- Implant extrusion	1	0.03	631.90	n/a	631.90	19.15	1	0.03	759.58	n/a	759.58	25.32	-127.68	-6.17
CUMULATIVE					39211.05	1188.21					40279.26	1342.64	-1662.21	-154.43

Discussion

In this health cost analysis, the mean cost per patient were compared between the MIPS and LITT-P technique in a randomized controlled trial cohort during long-term 22 months follow-up. A difference in mean cost per patient of € 77.83 in favour of the MIPS was found. Additionally, different scenarios were explored, i.e. all patients operated under general or local anaesthesia and mutation of the number of implant loss to the current situation using the MIPS with modified drill system. In all these scenarios, the differences in mean cost per patient were also in favour of the MIPS.

Currently, the research in the development of BCD surgery is focussing on the minimally invasive punch-only techniques like the standardized MIPS in comparison with the most widespread used LITT-P. The MIPS shows promising outcomes in terms of safety, complications, surgical results and quality.[27-34] An important factor that should be included in the comparison between these two surgical procedures is the health economic analysis. Our study is the first health economic cost analysis that gives the valuable insight in the difference in mean costs per patients after long-term follow-up between the MIPS and LITT-P.

There are some relevant points to discuss with respect to this cost analysis. First of all, this study identified all costs in the peroperative and postoperative section within the healthcare system / perspective. However, there are more costs. For example, patients and their families will have financial costs (e.g. expenses for travelling and informal care for relatives). Also, other sectors in the society could have costs by productivity losses (e.g. absence of their employee after surgery or for outpatient appointments). Nevertheless, these costs, not included in this analysis, apply for both techniques. It is therefore expected that a further evaluation of these cost will not influence the outcome of the results.

Secondly, the difference in price of surgery between general and local anesthesia is relatively small in this cost analysis. The reason for this is that all surgeries were performed in a fully equipped operation room, including staff. In other words, the only difference between costs of local and general anesthesia was the fee of the anesthesiologist. However, both MIPS and LITT-P are procedures that could be performed in an operation unit in outpatient setting. This would reduce costs for both procedures and create a significantly more marked difference

between costs for local versus general anesthesia. Moreover, if the costs for local anesthesia per time unit are lower, the difference in mean cost per patient between MIPS and LITT-P performed under local anesthesia will be less outspoken.

Furthermore, the outpatient visits are relatively high in both cohorts. The main reason is the trial set-up in which patients had standard follow-up at 9 days, 21 days, 3 months, 1 year and 2 years. There may be less standard follow-up appointments in a clinical (i.e. non-trial) setting. This will lead to a reduction in costs. Considering this applies for both techniques, it is not expected that this will influence the results of this study.

Finally, the extrusion rate of implants in the MIPS is relatively high in this study. Possible explanations are the usage of the first generation surgical kit and technique. Moreover, the MIPS was introduced only shortly before the start of this study, so this MIPS cohort reflects the first group of procedures and patients operated with the MIPS. A recent study of Caspers et al. showed that implant loss with the MIPS using the new modified drill system is only 4.0 %.[40] The fewer implant loss will lead to less costs per patient for the MIPS and an even larger difference between the MIPS and LITT-P (as demonstrated in one of our scenarios).

In the literature, recently, Kruyt et al. published a cost-benefit analysis for evaluation of percutaneous BCDs. A cost estimate was provided comparing multiple current generation BCDs with the previous generation. The conclusion was that wide implant diameter implants were more cost-beneficial. Though the purchase prices were higher, there were fewer complication-related costs.[41] Nevertheless, different surgical techniques were not taken into account and implants placed with the MIPS technique were not included. In comparison with our study, the same costs in the peroperative and postoperative course were identified. In our study, also costs for admission to patient ward, systemic antibiotic treatment and abutment change/removal were taken into account. The most remarkable differences in price was for skin revision surgery, because this was performed in our study in outpatient setting (instead of operation room). Also, the price per hour of the surgery did differ notably between the studies. This may be inherent to the fact that prices from two different cost administration (other academic hospitals) were used.

In conclusion, this cost analysis shows that the difference between the MIPS and LITT-P in mean cost per patient is € 77.83 in favour of the MIPS after long-term follow-up. In combination with the comparable or favourable results in safety, complications, quality of life and cosmetics found in previous studies, the MIPS is economically responsible and could be a promising technique for the future.

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8

SUMMARY AND DISCUSSION

Bone conduction devices (BCDs) are an important option for hearing rehabilitation in patients with uni- and bilateral conductive or mixed hearing loss, with an intolerance or inability to wear conventional hearing aids,[1-3] or in patients with single-sided deafness[4]. Last decades, the surgery for implantation of percutaneous BCDs has been evolved to more minimally invasive procedures. Nowadays, the most widespread used procedure is the linear incision technique with tissue preservation (LITT-P)[5]. There is also a trend to use punch only techniques like the standardized Minimally Invasive Ponto Surgery (MIPS) procedure by Oticon Medical AB[6]. This thesis focusses on the development of these minimally invasive surgical techniques in order to substantiate an evidence based fundament.

In *Chapter 2*, we performed a retrospective cohort study to identify if there are differences in soft tissue reactions and skin thickening between implantation of the BCD using the dermatome or linear incision technique with soft tissue reduction (LITT-R). In the group of patients operated with the dermatome technique, a soft tissue reaction (i.e. Holgers ≥ 1) was registered in 18 persons (40.9 %) compared to 36 persons (40.9 %) in the group of the LITT-R. Adverse soft tissue reactions (i.e. Holgers ≥ 2) were noticed in 9 patients (20.5 %) and 19 patients (21.6 %). Skin thickening was seen in 14 patients (31.8 %) in the dermatome and 11 patients (12.5 %) in the LITT-R cohort.

These results showed no significant difference in (adverse) soft tissue reactions between these two surgical procedures, tough skin thickening was noticed significantly more after the dermatome technique. Also, patients with risk factors for soft tissue problems and previous generation implants were allocated significantly more to the LITT-R cohort. This could cause an underestimation of the difference in soft tissue related problems in favor of the LITT-R. Based on the combination of no difference or possible more (adverse) soft tissue reactions after the dermatome technique and the significantly higher incidence of skin thickening, the LITT-R should be advocated.

This conclusion was in accordance with the literature. Studies regarding the dermatome technique reported an overall higher rate of skin problems[7-9] compared to the LITT-R[10,11], although methodological variability could influence these outcomes and impair adequate comparison. The direct comparison of patients operated with the dermatome technique or LITT-R in our study contributed to more solid support for the LITT-R.

Within the LITT-R, the implant could be placed inside or outside of the line of incision. There was little known about this step in the surgical procedure. In *Chapter 3,* we aimed to address this question in terms of soft tissue reactions. In our large scale retrospective cohort study, a Holgers ≥ 1 was noticed in 70 implants (60.9 %) placed inside the line of incision and 47 implants (49.0 %) placed outside the line of incision. The registration of adverse soft tissue reactions (Holgers ≥ 2) was in 20 implants (17.4 %) versus 17 implants (17.7 %). These differences were not significant, so these post-surgical (adverse) soft tissue reactions did not indicate a preference for placement of the skin-penetrating abutment in the procedure of the LITT-R.

Previous decade, Oticon Medical AB (Askim, Sweden) and Cochlear (Mölnlycke, Sweden) introduced new implants: the Ponto Wide implant and BIA400, respectively. Both these new implants could offer more stability[12,13], which led to the possibility to use longer abutments safely. This development created the opportunity to use the linear incision procedure without subcutaneous tissue removal. *Chapter 4* showed our retrospective cohort study comparing the LITT-R with the linear incision technique with tissue preservation (LITT-P) in surgical outcomes. A soft tissue reaction was registered in 16 implants (27.6 %) in the LITT-P and 28 implants (33.7 %) in the LITT-R cohort within the first 2 years of follow-up ($p = 0.679$). Adverse soft tissue reaction (Holgers ≥2) were encountered in two patients (3.4%) and in 16 patients (19.2%) within the same timeframe ($p = 0.040$). Skin thickening was noticed in 11 implants (19.0 %) versus seven implants (8.4 %) after LITT-P and LITT-R ($p = 0.024$), respectively, with successful treatment in all cases. Wound dehiscence was not encountered after the LITT-P but seen in 28 implants (33.7 %) after surgery following the LITT-R. Finally, the rate of implant extrusion was 4.8 % in LITT-R group after a median follow-up of 74.0 months. No implants were lost in the LITT-P after a median follow-up of 16.5 months.

This study substantiated the preference of the LITT-P over the LITT-R. Although there are more cases of skin thickening in the LITT-P cohort, this can be outweighed with the better outcomes in adverse soft tissue reactions and wound dehiscence. A consideration in the interpretation of this conclusion should be the retrospective nature of this study. However, the large size of the cohorts with long-term follow-up, comparable background characteristics between patients in these cohorts and one surgeon performing both techniques (i.e. minimizing other possible perioperative difference in approach) are important strengths of

our study. Moreover, the LITT-P showed in previous studies already favorable results in less numbness, shorter surgical time and cosmetics.[14-24]

Last years, the LITT-P became most widespread used based on the aforementioned beneficial outcomes. The next surgical innovation was the introduction of punch only techniques, like the standardized Minimally Invasive Ponto Surgery (MIPS). In *Chapter 5*, we described the 22 months results from our multicenter randomized controlled trial comparing the LITT-P with the MIPS. No difference was found between these techniques in (adverse) soft tissue reactions in both the intention-to-treat and per protocol analyses. Also, there were no differences in wound dehiscence, skin level, soft tissue overgrowth, pain and overall quality of life.

The MIPS cohort had better results on cosmetic scores and skin sagging. A note is that these cosmetic outcomes are scored by the surgeon and were relatively favorable in both cohorts. Patient satisfaction of the cosmetic results with (or without) processor did not differ between the groups. Skin sensibility loss was less after the MIPS until three months of follow-up. Previously, the short-term results of this randomized controlled trial did already show a significantly shorter surgical time for the MIPS.[25]

The Implant Stability Quotient (ISQ) was higher in the LITT-P cohort for different abutment lengths at various intervals in time during follow-up. The clinical relevance of difference in ISQ value and its link to osseointegration are a topic of debate.[26] However, it cannot be excluded that these higher ISQ values might be an indication of better osseointegration after the LITT-P procedure. This may relate to the, although not statistically significant, higher rate of implant extrusion in the MIPS group (n = 5, 15.2 %) compared to the LITT-P cohort (n= 1, 3.3 %). Delayed or less osseointegration might explain this higher proportion of lost implants, which is also relatively high in comparison with other studies[11,27,28]. In our manuscript, we postulated some hypotheses. First of all, there is less exposure at the implant site during surgery with punch only techniques compared to open approaches. This lack of visibility could lead to angulated and/or incomplete insertion of the implant. Secondly, the smaller incision will lead to less access for (external) irrigation with a risk of excessive heat generation. This will have a negative effect on the bone ergo osseointegration. A third possibility might be entrapment of soft tissue fragments in the osteotomy during insertion of implant (despite using a canula).

In conclusion, these long-term outcomes of our multicenter randomize controlled trial demonstrate favorable results for both surgical procedures. The MIPS is promising with some benefits over the LITT-P. Concerns regarding osseointegration and implant extrusion may be overcome with future research guided by the mentioned hypothesis.

The development of a new drilling system for the MIPS procedure, called MONO, was initiated by the hypothesis of less osseointegration by extreme heat generation due to the limited punch-only incision. In the MONO system, the final osteotomy for a 4 mm implant is created in only one single drilling step. This is in contrast to the LITT-P and MIPS systems, where a three-step drilling sequence is employed. The rationale was reduction of drilling time with fewer heat generation and associated undesirable effects on the bone. Since there is no stepwise deepening and widening of the osteotomy in MONO, it is crucial to evaluate the behaviour of the MONO drill bit when encountering the dura. *Chapter 6* showed our ex vivo experimental study on cadaveric, fresh frozen, human temporal bone samples. The MONO drill bit was compared to the guide drills used for the LITT-P and MIPS techniques in terms of the dura response to drill trauma.
The results revealed that for a drill depth exceeding the mastoid bone thickness by not more than 1 mm, damage to the dura was nonexistent or very limited. For a drill depth exceeding bone thickness with 2 mm, the MONO drill resulted in less penetration than the guide drills of the systems for LITT-P an MIPS surgery. Irrespective of the drilling system, the dura will be penetrated when exceeding the mastoid bone thickness with more than 2 mm.
The conclusion of these results was that the MONO system is not more inclined to penetrate the dura than the conventional LITT-P and MIPS systems. It is valuable to mention that the full depth of the osteotomy in the MONO procedure is 4.75 mm and previous research showed that 95 % of adults have a bone thickness of 5 mm or more in the region of BCD implantation.[29] This means that the MONO procedure should be considered a safe option for adult population. A recent systematic review stated that in about 6 % of the BCD surgeries the mastoid bone is penetrated. There was no indication of higher complication rates in case of exposure of dura.[30] Furthermore, the penetration of the mastoid bone followed by penetration of the dura, with a resulting cerebrospinal fluid leak, is reported in the literature with a frequency of 0.3% of the cases. All of these cases were without any serious adverse events in conjunction with this.[30]

Apart from the aforementioned favourable outcomes in quality, safety and surgical results of the MIPS, from societal perspective, it is also important to take the costs and resource into account when introducing a new and/or alternative surgical technique. A health economic study can be executed to improve consideration of benefits, harms and costs of interventions and contribute to informed decision making and allocating our health care resources. Even in the years before the COVID-19 pandemic, the costs for health care were 77.2 billion (year 2018) and 80.9 billion euros (2019) in the Netherlands (both years around 10 % of the gross domestic product).[31]

To the best of our knowledge, there are no previous well-designed health economic studies evaluating differences in costs between the MIPS and LITT-P. *Chapter 7* presented our health economic cost analysis to identify differences in mean cost per patient between the MIPS and LITT-P technique in our randomized controlled trial cohort (from *Chapter 5*). All costs in the perioperative and postoperative routing within the health care system were considered during long-term follow-up of 22 months, which led to a difference in mean cost per patient between both techniques of € 77.83 in favour of the MIPS. Additional scenario cost analysis were performed exploring the situation in case all patients were operated under general or local anesthesia. This showed a difference in mean cost per patient of respectively € 93.95 and € 62.49, both also in favor of the MIPS. In the final scenario, the implant loss was mutated to the more realistic implant loss of 4.0 % for the MIPS, based on the most recent study using the modified drill system[32]. A difference in mean cost per patient of €154.43 in favor of the MIPS was found. It can be concluded that the MIPS is an economically responsible technique for placement of percutaneous BCDs.

Surgical techniques in bone conduction devices have proved to be a dynamic field inspiring researchers around the world. Ongoing developments should be expected. In the context of future perspectives, first of all, the MIPS could be an interesting technique to be more widespread used based on the combination of similar or more favorable results compared to the LITT-P in safety, complications, soft tissue related problems, surgical time, quality of life, cosmetics and health economic costs. Concerns regarding osseointegration and implant extrusion are already current topics of research, which can be illustrated by our experimental study in *Chapter 6*. Secondly, this more minimally invasive surgery combined with better consideration for the health economic aspects may lead to perform BCD surgery more generally in an outpatient (operation room) setting. Finally, more research with patient

related outcomes measures (e.g. quality of life or patient satisfaction) and attention for health economic perspectives will lead to better insights to substantiate our choices for surgical techniques.

Another interesting trend for the future which should be mentioned, are the active transcutaneous bone conduction implants (atBCIs). An atBCI consists of an external sound processor and a transducer which is implanted in direct contact to the temporal bone underneath the skin. The signal is transmitted over the skin via an (analog or digital) induction link. The transducer implant generates mechanical vibrations to the bone.[33,34] Examples are BoneBridge (MED-EL, Innsbruck, Austria) and Osia (Cochlear, Mölnlycke, Sweden). The atBCIs reflect the tendency towards bone conduction hearing solutions without breach of the integrity of the skin. This could avoid several complications including soft tissue reactions, skin overgrowth/sagging and implant extrusion.[33-35] Several cohort and case control studies in recent years do show low complication rates in combination with similar audiological improvements in quiet and noise[34,35] and favorable patient satisfaction reports[34,36]. A critical note is, however, the more invasive nature of the surgical procedure compared to percutaneous BCDs.[33] Moreover, the costs of implant and surgery are more expensive in atBCIs. It will be interesting how these pros and contras are outweighed in the near future and could change the field of bone conduction devices.

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9

NEDERLANDSE SAMENVATTING

In 1977 werd door Tjellström het eerste botverankerde hoortoestel, oftewel bone conduction device (BCD), succesvol geïmplanteerd. Deze BCDs stimuleren de cochlea middels het principe van beengeleiding. Een BCD bestaat uit een titanium implantaat welke retro-auriculair in het os temporale geplaatst wordt. Op het implantaat wordt een koppelstuk, een abutment, bevestigd. Dit abutment komt door de huid heen en hierop kan een geluidsprocessor geplaatst worden. Deze processor zet geluidsgolven om in trillingen die vervolgens via het abutment/implantaat worden doorgegeven naar de schedel en het binnenoor (cochlea).

BCDs zijn een belangrijke optie voor gehoorrehabilitatie bij patiënten met een uni- en bilateraal conductief of gemengd gehoorverlies met een intolerantie of onmogelijkheid tot het dragen van conventionele hoortoestellen. Tevens is er een indicatiegebied voor patiënten met eenzijdige doofheid. Afgelopen decennia hebben de chirurgische technieken voor implantatie van percutane BCDs zich steeds verder ontwikkeld naar meer minimaal invasieve procedures. De lineaire incisie techniek met weefselpreservatie (LITT-P) wordt op dit moment in de meeste klinieken toegepast. Daarnaast is er een trend naar zogenoemde “punch only” technieken, zoals de gestandaardiseerde Minimally Invasive Ponto Surgery (MIPS) procedure van Oticon Medical AB. Dit proefschrift richt zich op de ontwikkeling van minimaal invasieve chirurgische technieken voor percutane BCD implantatie met als doel bij te dragen aan het wetenschappelijke fundament.

In *Hoofdstuk 2* voerden wij een retrospectieve cohortstudie uit om de dermatoom techniek met de lineaire incisie techniek met weefselreductie (LITT-R) te vergelijken. Een wekedelen reactie (Holgers graad ≥ 1) en een klinisch relevante wekedelen reactie (Holgers graad ≥ 2) werd gezien in een vergelijkbaar percentage van de patiënten in beide groepen. Verdikking van de huid werd significant vaker gezien bij patiënten in het dermatoom cohort (31,8 % versus 12,5 %, p = 0.001). Aangezien patiënten met risicofactoren voor wekedelen complicaties significant vaker in het LITT-R cohort bleken te zitten, kan het verschil in wekedelen reacties bovendien nog een onderschatting zijn ten faveure van de LITT-R. De combinatie van geen verschil of mogelijk meer (klinisch relevante) wekedelen reacties na de dermatoom techniek en de significant hogere incidentie van verdikking van huid leidt tot de aanbeveling van de LITT-R als procedure van keuze. Dit was in lijn met het beeld uit de literatuur.

Tijdens de chirurgische procedure van de LITT-R kan het implantaat binnen of buiten de incisie worden geplaatst. Aangezien dit een kennishiaat is, hebben wij een grootschalige retrospectieve studie uitgevoerd naar mogelijke verschillen in (klinisch) relevante wekedelen reacties. In *Hoofdstuk 3* worden de resultaten weergegeven, waarbij bleek dat er geen significant verschillen zijn tussen de beide cohorten. Op basis van deze postoperatieve wekedelen reacties kan dus geen voorkeur voor een van beide benaderingen binnen de LITT-R worden uitgesproken.

In *Hoofdstuk 4* wordt onze retrospectieve cohortstudie beschreven welke de LITT-R vergelijkt met de LITT-P op het gebied van chirurgische (postoperatieve) uitkomsten. Klinisch relevante wekedelen reacties (Holgers graad ≥2) kwamen significant vaker voor bij patiënten na de LITT-R in de eerste twee jaren follow-up (19.2 % versus 3.4 %, $p = 0.040$). Wonddehiscentie bleek eveneens significant vaker voor te komen na de LITT-R procedure (33.7 % versus 0 %). Verdikking van de huid bleek significant meer in het LITT-P cohort waargenomen te worden (19.0 % versus 8.4 %, $p = 0.024$). De resultaten uit deze studie onderbouwen de voorkeur voor de LITT-P boven de LITT-R. Hoewel verdikking van de huid vaker voorkomt na de LITT-P weegt dit niet op tegen de beter uitkomsten qua klinisch relevante wekedelen reacties en wonddehiscentie. Tevens bleek uit eerdere literatuur al de gunstigere uitkomsten van de LITT-P op het gebied van sensibiliteitsverlies, duur van de ingreep en cosmetiek.

De vergelijking tussen LITT-P en MIPS op de lange termijn staat centraal in *Hoofdstuk 5*. De resultaten van de 22 maanden follow-up van onze randomized controlled trial werden uiteengezet. Er bleek geen verschil in het optreden van (klinisch relevante) wekedelen reacties binnen zowel de intention-to-treat als de per protocol analyse. Daarnaast waren er geen verschillen in wonddehiscentie, gemiddeld huidniveau, huidovergroei, pijn en algeheel kwaliteit van leven. De MIPS groep toonde betere resultaten qua cosmetische scores, huidexces en (op korte termijn) sensibiliteitsverlies. Eerder werd binnen deze studie al een significant kortere duur van de operatie aangetoond bij de ingreep middels MIPS. In de LITT-P groep bleek er een significant hogere Implant Stability Quotient (ISQ) te worden waargenomen voor verscheidene abutmentlengtes tijdens diverse intervallen in de follow-up. Dit zou eventueel verband kunnen houden met het hogere, hoewel niet-significant verschillende, implantaatverlies in de MIPS groep (15.2 % versus 3.3 %). Meerdere hypothesen werden besproken: verminderde peroperatieve expositie waardoor groter risico op scheve en/of

incomplete insertie, kleinere incisie met meer kans op excessieve hittevorming en beknelling van wekedelen in de osteotomie gedurende het proces van implantatie. Samenvattend toonde deze lange termijn resultaten gunstige uitkomsten voor zowel de MIPS als LITT-P, waarbij de MIPS veelbelovend is met bepaalde voordelen ten opzichte van de LITT-P doch als aandachtspunt osseointegratie en implantaatverlies heeft.

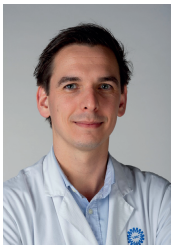
Vanuit deze aandachtspunten zijn er verscheidene innovaties geweest waaronder de ontwikkeling van een nieuw boorsysteem voor de MIPS procedure, genaamd MONO. *Hoofdstuk 6* toont ons ex vivo experimenteel onderzoek in humaan temporaal bot ter evaluatie van de veiligheid van het MONO boorstuk bij het aanboren van de dura. Er werd een vergelijking gemaakt tussen het traumatisch effect door aanboren met het boorstuk van de MONO ten opzichte van het boorstuk van het (conventionele) MIPS en LITT-P systeem. De resultaten toonden dat er bij alle boorsystemen geen of zeer beperkte schade was aan de dura indien de boordiepte de botdikte van het mastoïd niet met meer dan 1 mm overschreed. Bij een boordiepte die de botdikte van het mastoïd met 2 mm overschreed, resulteerde het MONO boorsysteem in minder penetratie van de dura in vergelijking met de andere systemen. In het geval van een boordiepte die de botdikte van het mastoïd met meer dan 2 mm overschreed, bleek de dura gepenetreerd te worden ongeacht het boorsysteem. Hieruit kon geconcludeerd worden dat het MONO systeem dus niet schadelijker is ten opzichte van dura in vergelijking met de MIPS en LITT-P boorsystemen.

Naast de gunstige uitkomsten van de MIPS inzake kwaliteit, veiligheid en chirurgische resultaten is het ook van belang om kosten en (financiële) middelen te beschouwen bij de introductie van een nieuwe/alternatieve chirurgische techniek. *Hoofdstuk 7* beschrijft de eerste gezondheidseconomische kostenanalyse tussen de MIPS en LITT-P. Alle kosten in het gehele perioperatieve en postoperatieve traject werden in beschouwing genomen binnen ons randomized controlled trial cohort tijdens de volledige follow-up van 22 maanden. Er was een verschil in gemiddelde kosten per patiënt van € 77,83 tussen beide technieken in het voordeel van de MIPS. Additionele scenario's werden geanalyseerd waarin patiënten onder louter algehele of lokale anesthesie werden geopereerd en het implantaatverlies werd aangepast naar meest recente literatuurgegevens. Hieruit bleek een verschil in gemiddelde kosten per patiënt van respectievelijk € 93,95, € 62,49 en € 154,43 ten faveure van eveneens

de MIPS. Concluderend is de MIPS een economisch verantwoorde techniek voor implantatie van percutane BCDs.

Het onderzoeksveld van de chirurgische technieken voor implantatie van BCDs is dynamisch en innovatief. In de toekomst mogen we dan ook zeker nog ontwikkelingen blijven verwachten. Deze toekomstperspectieven liggen op het gebied van verdere optimalisatie van de MIPS procedure, implementatie van gezondheidseconcomische aspecten rondom BCD chirurgie en toenemende aandacht voor patiënt gerelateerde uitkomstmaten in studies. Tot slot zijn de actieve transcutane BCDs een interessante trend, waarbij verscheidene complicaties van de besprokene percutane BCDs vermeden zouden kunnen worden.

Curriculum vitae



Ruben Mathé Strijbos was born on 26 April 1990 in Nijmegen, the Netherlands. He attended the Canisius College in Nijmegen and obtained his atheneum diploma (*cum laude*). Ruben started his study Medicine at the Radboud University in 2008. After the first year, he graduated for his propedeuse (*cum laude*). In the following years, he obtained his Bachelor and Master degree in Medicine at the Radboud University in 2015. During his study Medicine, Ruben participated in multiple committees within the Faculty of Medicine and had a fulltime board membership of the Medical Study Association Nijmegen (2010-2011). He did his senior internships at the department of Otorhinolaryngology (including research internship) and General Surgery.

After completing his study Medicine, Ruben started working as a surgical resident at the Jeroen Bosch Hospital in 's-Hertogenbosch. The field of Otorhinolaryngology remained his passion and Ruben continued his research into surgical techniques for bone conduction devices. He got the opportunity to continue this research as a PhD project in 2019 under the supervision of dr. S.J.H. Bom, dr. L.V. Straatman, prof. dr. M.K.S. Hol and prof. dr. R.J. Stokroos. In the same period he worked as an otorhinolaryngology resident (not in training) at the Deventer Hospital to further acquire valuable clinical experience. In January 2020, he started his residency at the Department of Otorhinolaryngology and Head & Neck Surgery at the University Medical Center Utrecht under supervision of drs. I. Ligtenberg- van der Drift and prof. dr. R.J. Stokroos. He completed parts of his training at the Meander Medical Center in Amersfoort (supervised by dr. E.H. van den Akker), Deventer Hospital (supervised by dr. S.J.H. Bom) and Gelre Hospital Apeldoorn (supervised by prof. dr. T.D. Bruintjes).

Ruben lives together with his wife Marlon and their daughters Saar (January 2020) and Fleur (September 2021).

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