Innovations in stapes surgery

Doctoral (PhD) Dissertation

Author: Alexandros Koukkoullis MD

Doctoral School Leader: Lajos Bogár med. habil. PhD

Program Leader: András Vereczkei med. habil. PhD

Supervisor: Péter Révész MD, PhD

Doctoral School of Clinical Medical Sciences

Medical School, University of Pécs, Hungary

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1 ABBREVIATIONS

ABG:	air-bone gap
AC:	air conduction
AI:	artificial incus
BAHAs:	bone anchored hearing aids
BC:	bone conduction
BTE:	behind the ear
CBCT:	cone beam computed tomography
CI:	confidence interval
CIs:	Cochlear Implants
CO_2:	Carbon Dioxide
EMG:	Electromyogenic
Erb:YAG:	Erbium-doped yttrium aluminium garnet
HRCT:	high resolution computed tomography
I-S:	incudostapedial
KTP:	Potassium Titanyl Phosphate
LP:	long process
MEI:	Middle Ear Implant
MRI:	Magnetic Resonance Imaging
NOS:	Newcastle-Ottawa scale
OR:	odds ratio
PRISMA:	preferred reporting items for systematic reviews and meta-analysis
PTA:	pure tone audiometry
SD:	standard deviation

SSCDS: superior semicircular canal dehiscence syndrome

VEMP: vestibular evoked myogenic potential

VSB: Vibrant Sound Bridge

WMD: weighted mean difference

2 OTOSCLEROSIS/OTOSPONGIOSIS

2.1 DISCOVERY

The study of otosclerosis can be traced back to as early as 1704 with Antonio Maria Valsalva, a Professor of Anatomy in Bologna, being the first to describe stapes fixation as a cause of hearing loss by performing post-mortem dissections on a deaf patient. He concluded that "osseous ankylosis of the stapes to the fenestra ovalis was one of the common causes of deafness" [1].

In 1873, Schwartze described a reddish hue on the cochlear promontory of patients with active otosclerosis (Schwartze sign)[2]. This active hyperaemic stage with increased vascularity caused remodelling of the bone (spongification), and was later named otospongiosis by Siebenmann[3]. It was assumed by Toynbee and others that chronic inflammatory mucosal changes in the middle ear resulted in secondary ankylosis of the stapes[4]. More than half a century later, in 1893, Adam Politzer described the histologic findings in 16 cases of stapes fixation[5]. His findings indicated that the hearing loss was due to a primary disorder of the labyrinthine capsule rather than an inflammatory change, which he referred to as otosclerosis.

2.2 EPIDEMIOLOGY

Otosclerosis is an autosomal-dominant hereditary disease with variable penetrance and expression. In adults, it is the most common cause of progressive conductive hearing loss, and of those affected two-thirds are women. It is associated with tinnitus and episodes of dizziness. Both ears can be affected in two thirds of the cases and there is a family history in about 50% of the cases[6].

Although pregnancy is known to exacerbate/accelerate the disease, an inciting event has not been identified yet. Other potential causes include endocrine, metabolic, infective, vascular, autoimmune and hormonal[6].

The disease, which can start in the early twenties, effects the bone that encapsulates the inner ear structures of hearing, the cochlea, and semicircular canals. This bone is called the otic capsule or the bony labyrinth[6].

2.3 PATHOPHYSIOLOGY (OTOSPONGIOSIS)

Bone absorption occurs due to osteoclastic activity, and new bone is deposited by osteoblasts. The osteocytes are located at the advancing edge of the lesion, which forms finger-like projections extending into the otic capsule. These lesions have vascular spaces in the centre. This results to disorganized bone rich in osteocytes with enlarged marrow spaces rich with blood vessels and connective tissue. The location and extent of these lesions vary, and some are small and do not involve the stapes. Inactive lesions appear sclerotic and grey. The advancing disease spreads across the stapedial annular ligament and causes stapedial fixation[6].

The type of hearing loss will depend on the focus of the lesion. In most of the cases is conductive (reduced sound energy reaching the inner ear) and involves mainly the anterior crus (anterior leg) of the stapes[6].

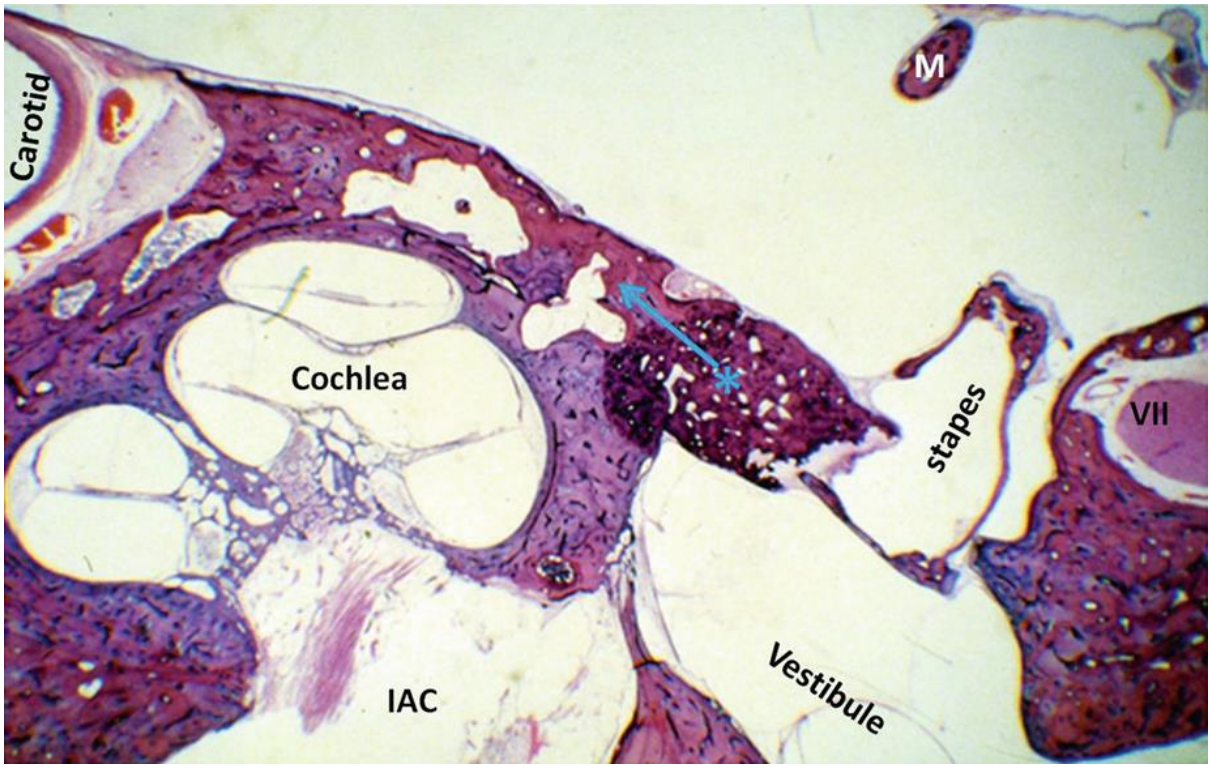

FIGURE 1: This is a slice through the middle and inner ear. Otosclerotic lesions have an affinity for haematoxylin, which makes the bone appear darker (*). Healthy surrounding bone has few viable osteocytes and chondrocytes. The osteoclasts are multinucleated and appear in the centre of the lesion[7].

2.4 CLINICAL EXAMINATION

Visual examination of the ear might not reveal any signs due to the lesion being hidden behind the tympanic membrane, and it is mainly done to exclude any other middle ear disease causing conductive hearing loss[6].

Rarely, a pink lesion can be seen through a thin tympanic membrane (Schwartze sign), referring to the active disease[2].

Tuning forks are the classical way of testing the hearing. Rinne test will indicate that the patient has *worse* hearing when the fork is held in the air next to the ear (air conduction) than when the fork is placed on the bone behind the ear (bone conduction). The patient will point to the worse affected ear when the fork is placed in the middle of the crown of the head with the Weber test (unless the hearing loss is equal). Weber and Rinne are performed with 256, 512 and 1024 Hz tuning forks and surgery for the worst affected ear is offered when at least two tuning forks are negative on the Rinne test[8]. Air-bone gaps of 25 to 40 dB, depending on frequency, are necessary for the Rinne to identify the presence of conductive components in most cases[9].

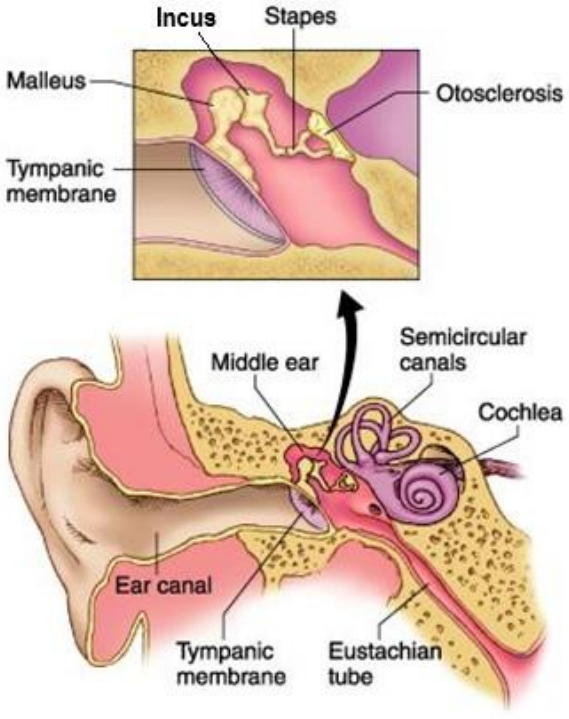

FIGURE 2: Basic anatomy of the ear with otosclerosis. The stapes is the last bone in the ossicular chain and the smallest of the body. Its footplate is connected to the inner ear via the oval window of the bony labyrinth. Otosclerosis begins on the bony labyrinth and expands onto the footplate and crura of the stapes[10].

2.5 AUDIOLOGY

Innovations in audiological instruments have all but replaced the tuning forks, although the tuning forks are still needed. A hearing assessment done in an audiological department is the main tool to diagnose otosclerosis[6].

2.5.1 Pure tone audiogram

Pure Tone Audiogram not only can it differentiate, but also measure conductive hearing (kinetic energy reaching the inner ear) and sensorineural hearing (the maximum kinetic energy that can be converted to electric impulses by the inner ear and reaches the brain) and plot them as line graphs[6].

The gap between the two lines is known as the ABG with air representing conductive hearing and bone representing sensorineural hearing. Surgical treatment in the case of otosclerosis aims to bring these two lines as close as possible to each other (reduction of the ABG) [6].

In 1950, Carhart reported bone conduction dip on the PTA approximately at 2kHz among patients with otosclerotic stapes fixation that disappeared after stapes surgery[11]. The frequency of the notch varies depending on the resonant frequency of the ossicular chain for bone-conducted signals. In humans, this is usually around the 2kHz frequency. It is not a true indicator of sensorineural hearing, and it is found in other conditions. Therefore, it is not pathognomonic of otosclerosis, but its presence would strongly indicate the disease[6].

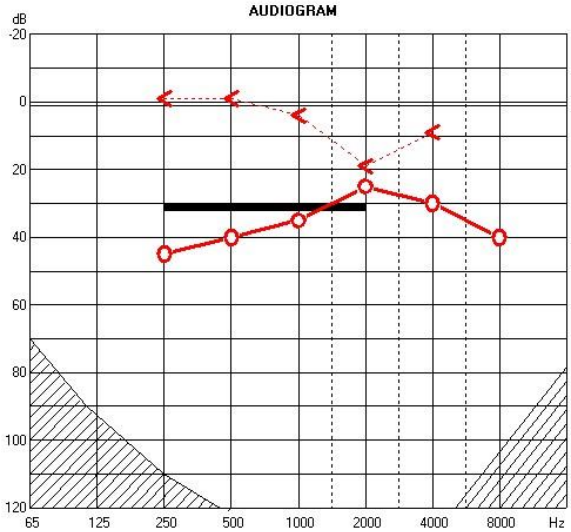

FIGURE 3: An example of a pure tone audiogram and the classical shape for an otosclerotic ear. The top line is the bone conduction, and the bottom line is the air conduction. The gap between them is the ABG. A downward drop of the bone conduction with an upward turn of the air line at 2 kHz is the Carhart's notch. The aim of the surgical treatment is to reduce the ABG to under 10 dB.

2.5.2 Acoustic Reflex Testing

Our body has protective mechanisms against loud sounds and one of these is the stapedial reflex. Transient muscle fixation of the stapes purposely occurs to sustained, loud noise exposure. This is done to minimise the kinetic energy reaching the inner ear and avoid organ damage[6].

The stapedial reflex can be tested and certain departments require it for diagnosis. Its absence would be an indication of fixed stapes on the affected side[6].

2.5.3 Multifrequency Tympanometry

This test indirectly measures the resonance of the ossicular chain which varies depending on the rigidity of the chain. A very mobile chain (ossicular discontinuity) will have a low resonance frequency while a fixed chain (otosclerosis) will have a higher resonance frequency[12].

A fixed stapes will increase the rigidity of the ossicular chain but again it is not pathognomonic of otosclerosis[12].

2.5.4 Speech Discrimination

This is the patient's ability to recognise speech at different loudness levels. If the patient only suffers from conductive hearing loss, then they should be able to understand what is said to them if the sound is loud enough[6].

While this test does not measure ossicular fixation, it is important. Poor speech discrimination would indicate that even if the ABG was reduced (improved hearing) the patient would not be able to understand speech any better. The benefit from the procedure will not be significant enough to justify its risks and therefore will not be offered to the patient[6].

2.5.5 Vestibular evoked myogenic potential

VEMP is a relatively recent vestibular function test performed by measuring surface electromyogenic responses over selected muscles, after stimulating one ear with repetitive pulse or click sound stimulation and averaging the reaction of the muscle electrical activity associated with each sound click or pulse [13]. It is not indicated for diagnosis or surgery, however may rule out other pathology, like SSDCS.

SSCDS is an uncommon syndrome due to an abnormal opening or dehiscence in the bony roof of the superior semicircular canal in the temporal bone. It can present with progressive conductive hearing loss like otosclerosis, leading to misdiagnosing the patient. VEMP is abnormal with SSCDS[13].

2.6 IMAGING

HRCT and CBCT are the imaging modalities of choice but are not required for diagnosis. Modern scanners can clearly picture the ossicles and even colour them for better visualisation.

They can improve diagnostic probability by excluding anatomical abnormalities and malleus fixation**,** assessing for any ossicular discontinuity, and even measuring the otospongiotic focus.

However, the radiology department should have a dedicated neurotology radiologist who would process many cases to maintain acceptable specificity and sensitivity[6].

2.7 NON-SURGICAL TREATMENT

2.7.1 Active monitoring (observation)

In the early stages, the hearing loss might be significant enough to be felt by the patient, but audiological assessment might not justify surgical intervention (ABG < 30 dB). Additionally, some patients will choose not to have the surgery due to fear of its complications[6].

In these cases, the patient is monitored with regular hearing assessments for deterioration of hearing. Surgery will be offered if hearing loss meets indication criteria, and the benefits of the procedure outweigh the risks[6].

2.7.2 Conservative treatment

External hearing aids are offered to patients with small ABG and to those who do not wish or cannot have surgery. However, as hearing deteriorates, so will the effectiveness of these hearing aids. Patients who have almost no hearing or have lost their hearing completely can be considered for a cochlear implant[6].

2.7.3 Surgical treatment

The main therapeutical choice is stapes surgery. However, rarely alternative surgical approaches may be required such as bone anchored implantable devices, middle ear implants or cochlear implants, based on patient conditions and the severity of hearing loss[6].

3 STAPES SURGERY

3.1 ADVANCEMENT THROUGH TIME

The progress of the stapes surgery can be classified into four stages or eras based either on the progression of surgical technique or by the discovery of antibiotics[14].

3.1.1 Mobilisation and early Stapedectomy

Surgery was initially focused in remobilising the ossicular chain by intra-operative manipulation of the stapes. Many consider Prospere Ménière's case of a patient who was able to temporarily improve his own hearing by tapping the stapes directly with a small gold rod as the first attempt to mobilise the stapes[15]. Pioneers included Kessel from Germany, Boucheron and Miot from France, Blake and Jack from the US, and Faraci from Italy[16].

The first description of stapes surgery is attributed to Johannes Kessel in 1876[17]. He erroneously assumed that the hearing loss associated with otosclerosis was the result of increased pressure in the inner ear fluids. Thus, he believed that by removing the stapes, he could relieve that pressure. His procedure was to make an incision to the posterior part of the tympanic membrane, separate the incus from the stapes, and then try to mobilize the stapes by applying pressure to its head from several directions. If this was not successful, he would remove the stapes altogether, essentially performing the first stapedectomy[18].

Many had followed Kessel's path with similar success. In the United States, Frederick L. Jack's method of treatment was to approach the middle ear cavity via tympanic membrane incision rather than a reflection of a tympanomeatal flap[19]. He reported that patients experienced improved hearing as the tympanic membrane healed over the oval window niche[14]. This was before the discovery of microscopes which offered better magnification and illumination, and therefore he would not reconstruct the ossicular chain.

A particularly interesting case of Jack's was a patient who had a double stapedectomy and 10 years later maintained a good hearing[20]. He described how 'the tympanic membrane had retracted in the healing process and created a moveable membrane over the oval window'.

However, any improvement was short lived as the abnormal bone would grow back again over the oval window and fix the stapes once more[14]. Furthermore, the force required to mobilise the stapes in advanced cases ended in a high rate of complications, such as deafness, and thus the procedure was abandoned with no real alternative for a long time[14]. Lastly, it was the era before antibiotics and the infection rate would have been high, but the rate of complications was underreported during that era[14].

3.1.2 Fenestration

It was Julius Lempert in 1938 who popularised stapes surgery once more, after he perfected the surgical techniques of fenestration by pioneers such as Gunnar Holmgren and Maurice Sourdille that focused on bypassing the stapes fixation to the natural oval window by creating another one (fenestration) on the otic capsule[21]. The theory was that the kinetic energy could be re-routed from the natural otic window to the fenestration, so it reaches the inner ear for conversion into neural impulses, closing the ABG.

Robert Bárány obtained good results with the fenestration of the posterior semicircular canal in 1910 while Maurice Sourdille in 1937 developed a novel technique called "tympano-labyrinthopexy" performed in 2 or 3 stages during aseptic conditions[22,23]. Lempert's single stage method involved fenestration of the lateral semicircular canal making it a far more attractive to surgeons. His results were similar if not better than Sourdille's.

However, this worked only for about two thirds of the patients and there was a significant number of cases with complications.

3.1.3 Intraoperative selection of treatment and the rediscovery of mobilization

Samuel Rosen further improved the technique by intra-operatively selecting on whom to perform the fenestration by confirming the fixation of the stapes[24]. Rosen, who attended one of Lempert's courses, wondered why the fenestration method did not work for all patients and considered that not all cases had a fixed stapes. He started confirming intraoperatively the fixation by gently pushing the stapes and improving the likelihood of a successful outcome.

While attempting to confirm fixation in a patient, he accidentally mobilised the stapes. The patient's hearing improved dramatically and thus Rosen rediscovered mobilization of the stapes as a treatment[10]. Many prominent surgeons of the time, such as William House, had adopted his methods with great success. Nonetheless, recurrence of stapes fixation and the complications due to the force needed to mobilize the stapes persisted, although with the advancement in middle ear instruments and the discovery of antibiotics, these would have been significantly less than past cases.

3.1.4 Stapedectomy

John Shea in 1956 added the last piece of the puzzle by removing the entire stapes with the footplate and replacing it with a plastic prosthesis[25].

Shea came across Jack's long-lost report describing how the patient was still hearing, even 10 years after double stapedectomy, most likely due to the tympanic membrane healing over the

oval window and creating a mobile membrane[20]. After reading the paper, Shea had realized the significance of Jack's procedure, and that it must be possible to remove and replace an otosclerotic stapes with a prosthesis.

His method was to remove the stapes and the footplate covering the oval window, covering the space with a harvested vein and attach a Teflon prosthesis to the incus and the oval window. As he removed the stapes with the footplate, this procedure became known stapedectomy and it is still used even now for certain cases. Today, it has been superseded by stapedotomy, which is the latest form of a procedure that keeps evolving.

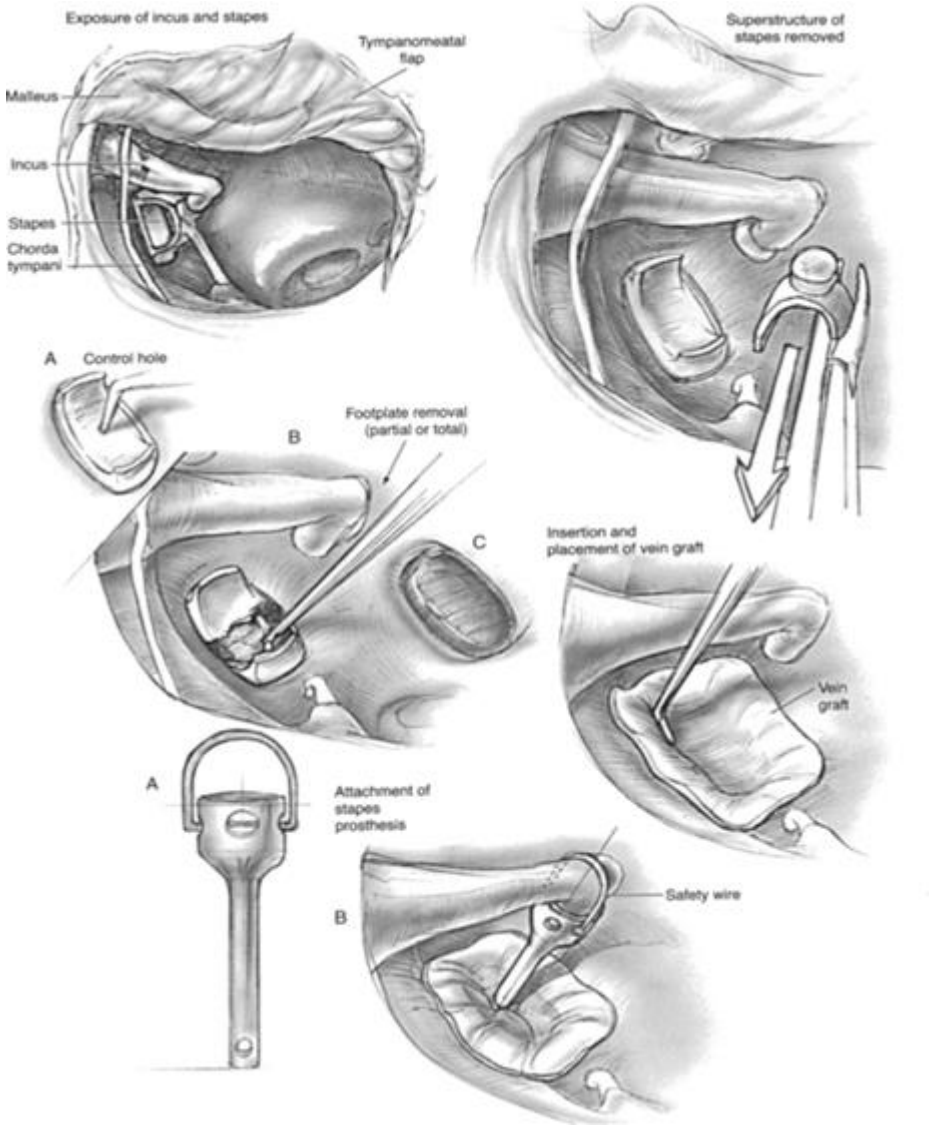

FIGURE 4: The steps for stapedectomy (partial or total) with a Robinson bucket handle prosthesis. The steps of the surgery are from top to bottom[26].

3.2 STAPEDOTOMY

3.2.1 Indications

The patient should have a PTA demonstrating a conductive or mixed hearing loss (sometimes with a Carhart's notch) with a large enough ABG and absent stapedial reflexes. The affected ear should be the worse hearing ear. Speech discrimination should be sufficient to justify the risk of the procedure. Prior to surgery, VEMP can be performed to rule out SSCDS but is not mandatory. Clinical examination should exclude other middle ear disease and the tympanic membrane should be intact. Imaging can help to confirm the clinical diagnosis or exclude other pathologies. Below we have listed the most common indications and contraindications[6,8,27].

Indicators	Contraindicators
• Progressive conductive hearing loss • Absent stapedial reflexes • Air-bone gap greater than 20 dB in at least three frequencies • Good speech discrimination • Worse hearing ear	• Perforated tympanic membrane • Better hearing or only hearing ear • Poor speech discrimination • Air-bone gap less than 20 dB in at least three frequencies • Ongoing middle ear disease

3.2.2 Procedure Overview

3.2.2.1 Anaesthesia

The procedure can be done under general anaesthesia or local anaesthesia. The latter may be preferred as the patient can feedback to the surgeon what they are sensing such as improvement in hearing or dizziness[6,8,27].

3.2.2.2 Tympanotomy

The middle ear is usually accessed via transcanal or endaural approach. When a transcanal approach is performed, an incision is done within the ear canal close to the tympanic membrane and the entire skin and membrane are lifted from the bone. When endaural approach is carried out, the skin incision is done in front of the root of the helix and continued into the posterior-superior part of the outer ear canal. Care must be taken when entering the middle ear so that the chorda tympani nerve, which supplies taste to the ipsilateral 2/3 of the tongue, is not injured. Also, care must be taken so as not to perforate tympanic membrane[6,8,27].

3.2.2.3 Visualisation

The mains structures (stapes, its footplate, the oval window and the facial nerve) must be within the operating view. Lateral atticotomy (bone removal) is usually performed to achieve the required view with care taken not injure the chorda tympani nerve[6,8,27].

3.2.2.4 Confirming fixation

Gently pushing of the ossicles to confirm fixation of the stapes. Fixation of the other ossicles due to another disease is rare but possible so their mobility must also be confirmed, otherwise the conductive hearing loss will persist[6,8,27].

3.2.2.5 Removal of stapes superstructure

There are multiple steps to this part, but the aim is to remove the stapes bone without the footplate. Care is taken not to injure the facial nerve, which passes near the footplate as this can cause facial weakness on the operated side. Beneath the otic capsule, there is the membranous labyrinth containing the perilymph. Care must be taken so the membrane is not ruptured and for fluid not to leak out, as this can result in permanent hearing loss[6,8,27].

3.2.2.6 Stapedotomy

A small hole (0.6-0.8 mm) is made through the posterior part of the footplate but taking care not to cause fracture. This step can be performed by laser, microdrill or manual perforator (pick) [6,8,27].

3.2.2.7 Prosthesis placement

Following the measurement of the distance between the long process of the incus and the stapedotomy hole, the correct size of prosthesis is chosen. One end of the prosthesis is placed into the stapedotomy hole and the other end is attached and crimped to the long process of the incus, bridging the gap between the incus and the vestibule. Any space around the hole is filled with tissue harvested from the surrounding. Finally, the mobility of the reconstructed ossicular chain is verified[6,8,27].

3.2.2.8 Closure

The tympanic membrane and skin are placed back to their original positions and the incision is allowed to heal on its own with the transcanal approach. If the endaural approach was performed, the external incision needs to be sutured. If the tympanic membrane has been previously perforated, then closure with a fascia or cartilage graft is done at this stage. The ear canal is filled with antibacterial material to avoid wound infection[6,8,27].

3.2.2.9 Follow-up

The patient is seen couple of weeks later to remove the antibacterial material and to assess the healing. They are seen once more about couple of months later, once healing is completed, to assess their hearing. Afterwards, they can have regular hearing assessments to ensure hearing is stable and for research purposes[6,8,27].

3.2.3 Possible complications

3.2.3.1 Dead ear

This term refers to a rare complication resulting in complete hearing loss and can occur due to perilymph leak, utricule injury, labyrinthitis or granuloma formation. Patient must be consulted about this possibility as they might choose to use hearing aids instead of undergoing surgery[6,8,27].

3.2.3.2 Facial Weakness

The nerve runs through the middle ear and close to the oval window. A facial nerve monitor may be used to assist to find the path of the nerve and demonstrate normal functional just before closure. The weakness is almost always transient, as it is extremely rare for the facial nerve to be severed but the patient must be consulted about the possibility[6,8,27].

3.2.3.3 Altered taste

The chorda tympani nerve is most of the time obstructing the operating view. Manipulation to marginalise the nerve is almost unavoidable during surgery. Like the facial weakness, the taste recovers in most cases except where the nerve was severed. This is more common than the facial nerve injury but still rare[6,8,27].

3.2.3.4 Dizziness

Excessive movement of the inner ear fluid will affect the balance apparatus of the ear. This is mainly due to manipulation of the ossicles and the footplate which results in large amounts of kinetic energy to be transmitted to the vestibule. Again, this is usually transient.

3.2.3.5 Tinnitus

Ringing in the ear is common but recovery is certain[6,8,27].

3.2.3.6 Pain

This is due to tissue damage, mainly the skin incision and bone removal to improve surgical view. The endoscopic approach requires smaller skin incision and rarely any bone removal. Thus, it should result in less pain[6,8,27].

3.2.3.7 Tympanic membrane perforation

Tympanic membrane perforation is common in the community and surgical closure (myringoplasty) is greatly more common than stapes surgery. Thus, although unfortunate, this is a minor complication that can be fixed during the surgery. An extra scar might be present to harvest the necessary graft[6,8,27].

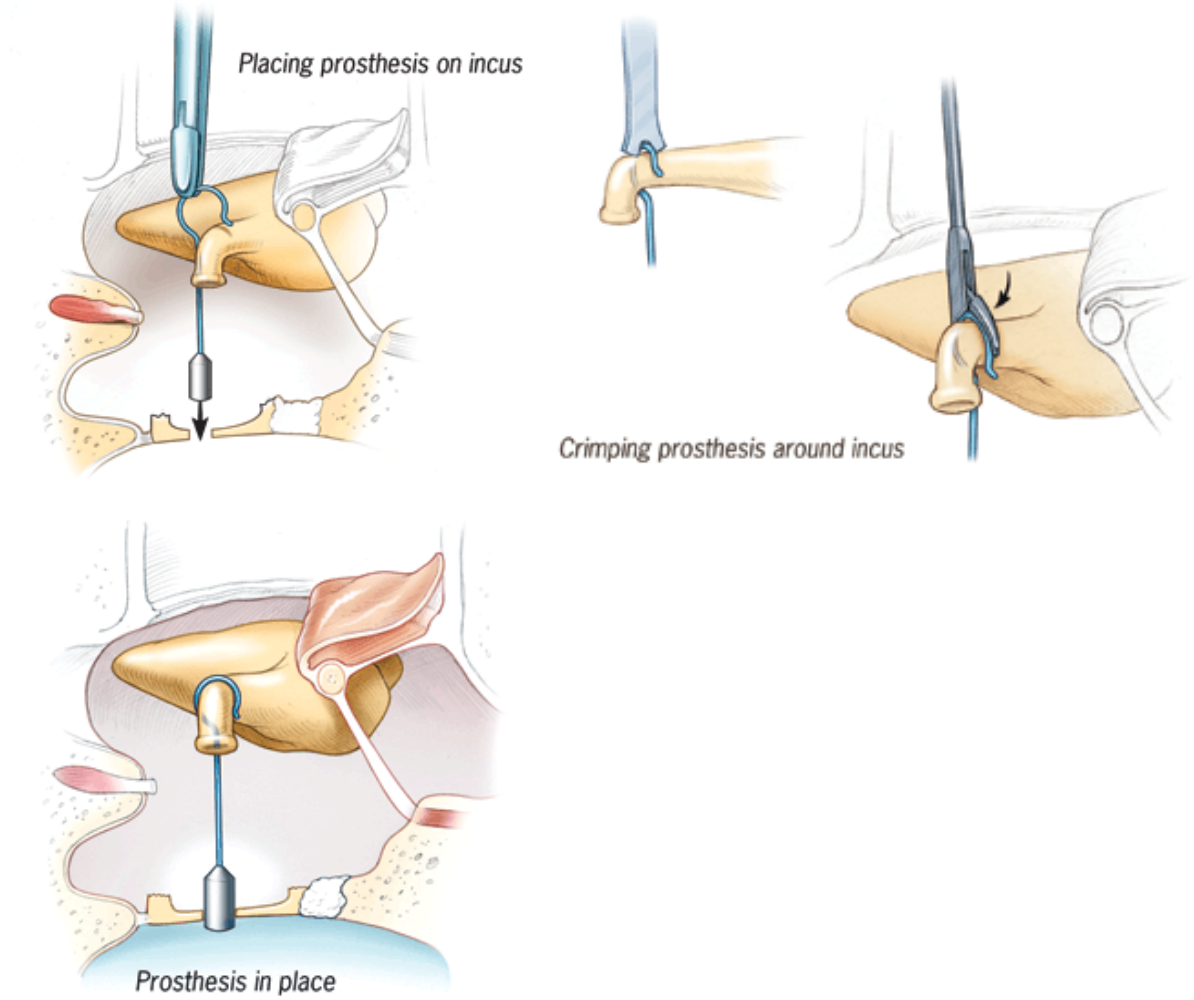

FIGURE 5: The basic steps of placing stapes prosthesis with crimping[28].

4 MAJOR INNOVATIONS IN STAPES EAR SURGERY

4.1 THE MICROSCOPE IN EAR SURGERY

The first descriptions of the microscope date back to the 17th century. However, these referred to the early compound (multiple lenses) monocular microscopes used to improve scientific observations in the laboratory setting. In addition, they had major imperfections which would not be resolved until the middle of the 19th century, to make them superior to the single lens microscope (sometimes referred to as the magnifying lens)[29].

Three scientists can be associated with the first use of a monocular microscope in otology: Kessel in 1872, Weber-Liel in 1876 and Czapski in 1888. Emilio de Rossi introduced the concept of stereopsis with the first to use a binocular microscope, even though this was single lens, in 1869. Nonetheless, these early microscopes were difficult to manoeuvre and not really used in practice[29].

Credited with the most important advances made in the field of optics and microscopes was the Zeiss factory, where Carl Zeiss, Ernst Abbe and Otto Schott were able to further the concept of stereopsis and create the first binocular microscope at the end of the 19th century[29].

In 1921, a Swedish otologist, Carl Olof Nylen, used a microscope he developed with engineer N. Pearson for the first time in ear surgery. This monocular microscope was rapidly replaced by a binocular microscope developed in 1922 by Nylen's colleague, Gunnar Holmgren, and the Zeiss factory. Holmgren used the microscope particularly for the fenestration technique in otosclerosis[29].

However, because of their limited field of vision, very short focal distance, poor light quality, and instability (they were mounted on the patient), these microscopes were not utilised by everybody. Most notably, Lempert and Sourdille preferred to use magnifying spectacles for the ear operations[29].

In 1951, Hans Littmann of the Zeiss Company developed a new microscope by partially collaborating with Horst Wullstein and Fritz Zöllner on new techniques in tympanoplasty and ossicular reconstruction. This new microscope could be mounted on a fixed stand with a mobile arm, allowing for fine movement. The light source was in the coaxial plane, had a selective magnification and a working focal length of 20cm (which could be changed to 25cm). This model (Zeiss Model I) was so successful that all subsequent models are based on it. It allowed for the development of tympanoplasties and stapes surgery[29].

4.2 THE HISTORY OF THE PROSTHESIS

It all begun in 1956 with Shea's newly devised microsurgical technique, the stapedectomy. A procedure in which an otosclerotic stapes was replaced with a prosthesis carved from Teflon fluoroplastic. Since then, more than 100 other stapes prostheses have been developed with innovations over the years in microsurgical technique, materials and technical properties used influenced the evolution of the prosthesis[30].

The basic physical requirement of a stapes prosthesis is to secure a connection between the mobile incus and the sealed perilymph in the oval window. "It must be long enough to stay in the fenestra but short enough not to intrude excessively within the vestibule and risk injury to the otolith organs"[30].

4.2.1 Technique

Shea initially performed a stapedectomy, covered the exposed oval window with a vein graft, inserted the prosthesis in the window on one end and attached it to the incus on the other. Later, stapedotomy required a small fenestra on to the footplate which could be covered after the insertion of the prosthesis and plugged with surrounding tissue such as fat or fascia. Stapedectomy is still being used for advanced case of otosclerosis today[30].

4.2.2 Material and shape

Several different materials have been used over time with surgeons experimenting with just as many different shapes to find the optimum combination. Teflon, steel, aluminium, gold and titanium have all been used either alone or in combination. The changes in the shape can be seen in the figure 6[30].

Previous notable changes in material are the use of titanium instead of gold and steel as they crimped better with the use of crimping forceps. The same study concluded that band-shaped loop was better than wired-shaped loops[31].

4.2.3 Complications

The main concern is the ability of the prosthesis to remain in place and not move with time which would cause hearing loss to recur. While positioning does depend on the shape, it is heavily influenced by surgical skill. The hook and piston shape are the most common but other prostheses can be used depending on the situation[30].

Incus can become necrosed if damaged due the procedure or if the prosthesis compromises the blood supply. This is known to happen with the crimping of the prosthesis. Newer models,

such as the NiTiBOND (Heinz Kurz, Dusslingen, Germany), use thermal memory to attach themselves and have a smaller contact area with the incus, minimizing the damage[30].

Furthermore, magnetic resonance imaging (MRI) scanners can move certain magnetic steel prostheses which is why other non-magnetic metals are more popular. The variation in the length was solved by measuring the distance needed and adjusting the prosthesis[30].

4.2.4 Prosthesis diameter

The diameter of the pistons used initially was 0.8mm and 0.6mm but it has with time become ever smaller, 0.4mm and 0.3m, to ease the procedure and to reduce the risk of inner ear damage. While some studies have found that the larger diameter offers a better air conduction improvement due to greater kinetic energy efficiency, others have found no difference[32,33,34,35].

Improvement was made in the way the prosthesis is fixed to the long incus process, resulting in different solutions like Teflon memory effect, platinum and gold band, titanium-gold clip prostheses or nickel-titanium alloy heat memory effect[30].

Eventually, the most decisive factor for successful surgery is surgical experience with a specific type of prosthesis and the expertise in the microsurgery technique[36]. Figure 7 shows the highlights of stapes surgery techniques[30].

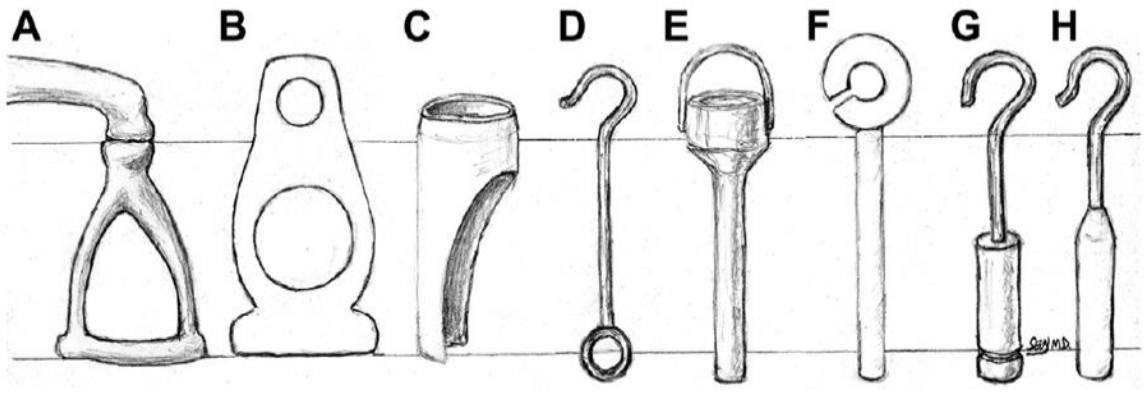

FIGURE 6: Different prosthesis over the years. Early and representative stapes prostheses. (A) Human stapes and incus long process; (B) first stapes prosthesis, Shea and Treace, carved Teflon fluoroplastic; (C) Shea strut, polyethylene; (D) House wire loop, stainless steel; (E) Robinson bucket handle, titanium; (F) fluoroplastic loop; (G) platinum wire hook, stainless steel piston; and (H) nitinol wire hook and fluoroplastic piston[30].

Stapes surgery technique highlights

Surgeon/ Inventor, Year	Prosthesis	Stapes	Graft/Material at Round Window	Attachment to Incus
Shea, 1956	Carved Teflon piston	Stapedectomy	Vein graft	Placed long process through hole
House, 1960	Wire loop, stainless steel	Stapedectomy	Vein graft	Crimp wire onto long process
McGee, 1960	Shepherd's crook + piston, stainless steel	Stapedectomy	Vein graft	Crimp wire (shepherd's crook) onto long process
Robinson, 1961	Bucket handle, stainless steel (now titanium)	Stapedectomy	Vein graft	Lift incus vs push prosthesis down, slide lenticular process into cup and bucket handle over long process
Schuknecht, 1962	Wire loop stainless steel, Gelfoam	Stapedectomy	Vein graft, Gelfoam at end of wire loop	Crimp wire onto long process
Shea, 1962 (popularized and later modified by Causse)	Teflon loop + piston	Stapedectomy	Vein graft	C-shaped hook onto long process, no crimping. Option to attach stapedial tendon to prosthesis
Silverstein, 1989	STAMP	Laser stapedotomy/ anterior crurectomy	Fat graft	I-S joint not divided, stapedial tendon preserved
Wengen, 1997	aWengen clip, titanium	Stapedotomy		Spring allows clipping onto LP without crimping
Knox, 1999	Nitinol heat-activated wire, Teflon piston	Stapedotomy		Place hook over long process, then heat-activated crimping; can use laser

FIGURE 7: Progressive changes in the prosthesis and the graft based on the type of surgery used[30]. Abbreviations: I-S, incudostapedial; LP, long process

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4.3 THE LASER IN STAPES SURGERY

Surgery of the middle ear is performed on barely visible structures in a space of about one cubic centimetre in size, necessitating the creation of appropriate equipment. The surgical microscope has undoubtedly improved the quality of the surgery by offering views needed to perform the surgery safer and more effectively.

At the start, the main tool used to create fenestration in the oval window was the surgical pick whose precision was very operator dependent. A stapedotomy could change into either partial or total stapedectomy as the footplate might fracture during fenestration. However, the microdrill and the laser have since improved on this precision with more accurately created windows for a better fitting with the prosthesis[37].

The laser microscope was first developed and used by Rodney C. Perkins in 1980s who used it 'to vaporize the stapes tendon, the posterior crus and a rosette of holes in the stapes footplate, pick any remaining bone to complete the fenestration, and then used an autogenous vein—stainless steel piston assembly to reconstruct the stapes portion of the ossicular chain'[37].

Perkins modified a Zeiss Model I operating microscope so that he would be able to guide the laser beam, just like his light, into his field of view. Such was the precision of the laser that he could target the tendons and parts of the stapes within the middle ear[37].

However, he was concerned that the 'laser beam might continue through the footplate and damage' the underlying structures. That is why initially he practised on cadaveric temporal bones to examine what effects the laser had on the surrounding tissues. He found that there was no damage to the inner ear structure as he feared and conclude this was due to 2 reasons. First, the laser beam, while made to converge on the surface of the footplate, it diverged afterwards, greatly reducing its power. Second, he used a very short burst which delivered a limited amount of energy to the tissue which then limited the depth of the damage. Another concern for Perkins was that 'the heat would cause currents within the inner ear liquid (perilymph) which would result in vertigo or even worse in sensorineural hearing damage'. This concern was also put to rest as no patient complained of intraoperative dizziness and sensorineural hearing loss was not reduced post-surgery[37].

Therefore, 'the ideal laser for stapes surgery should have high bone ablation efficiency, small tissue penetration depth to avoid damaging the underlying structures, low transfer of heat to the surrounding tissue and no or minimum acoustic side-effects (due to rapid and explosive

vaporization)'. In addition, they need a precise delivery method, such as the fibre optic cable, and visibility[38,39].

The Argon and Potassium Titanyl Phosphate (KTP) lasers have wavelengths in the visible spectrum and are absorbed by haemoglobin with good haemostasis. However, they are not well absorbed by bone leading to deeper penetration and radiation can spread to underlying structures. They can be delivered by fibre optic cable which some argue causes greater bean divergence and thus minimising penetration depth and underlying structure damage[38,39].

The Carbon Dioxide (CO_2) laser has a wavelength in the infrared spectrum and is not visible. It has a high bone absorption and therefore less depth penetration and potential damage to underlying structures. Until recently, the beam could only be delivered via micromanipulator placed on the microscope and as it was invisible it required a guiding visible laser beam. Newer models can be delivered via fibre optic cables, but their effectiveness is yet to be determined. There are higher temperatures involved due to high bone absorption that can affect the underlying structures[38,39].

Erbium-doped yttrium aluminium garnet (Erb: YAG) laser has a wavelength at the near infrared and can be delivered via optic fibres. It has a high bone absorption and reduced penetration and therefore reduced damage to surrounding tissues. It does have however poor coagulation capability and can lead to acoustic trauma[38,39].

Ultimately, the decision of which laser to use lies with the surgeons who might not have a choice as they are very expensive equipment and theatre staff needs to be trained on various safety measures.

4.4 IMPLANTABLE HEARING DEVICES

4.4.1 Bone Anchored Hearing Aids

BAHAs take advantage of the fact that sound can travel vial the skull to reach the inner ear, bypassing the outer and middle ear. They are indicated in conductive or mixed hearing loss where patients cannot use or cannot tolerate conventional hearing aids. Additionally, they can be used in single-sided deafness as the vibrations can reach the opposite functioning ear providing bi-directional hearing. Sensorineural hearing (cochlear hearing) levels should be at 65 dB or better. The procedure to implant them is simple and some can be done under local anaesthesia[40,41].

Devices such as the BAHA Connect (Cochlear, Australia) and the Ponto (Oticon Medical AB, Sweden) have a titanium screw implanted into the skull bone behind the ear which extends

through the skin (percutaneous). An external sound processor with a microphone can be attached on to the screw via an abutment and covert sound into vibrations similarly to the tuning fork[40,41].

Newer models such as the BAHA Attract (Cochlear, Australia) and Alpha MPO (Medtronic, USA) have a magnetic connection with no visible part protruding through the skin (transcutaneous). The sound processor attaches via an external magnet onto an internal magnet under the skin, and in turn this magnet is directly attached to the titanium screw[40,41].

The latest models such as the BAHA 5 SuperPower Attract (Cochlear, Australia) have the microphone/processor unit behind the ear, like conventional hearing aids. Signals travel via an external cable to a separate vibrator unit (actuator) which is attached magnetically to the titanium screw. This system is more powerful and can be used for hearing thresholds up to 65 dB[40,41].

Other systems such as the Bonebridge (Med-El, Austria) and Osia (Cochlear, Australia) also have a magnetic attachment. However, the magnetic fields are converted to electrical signals first which are processed by an internal processor and then relayed to an internal transducer embedded into the skull (like the titanium screw). In contrast to the titanium screw, the transducer can produce vibrations and hence it is an active device. Surgery to implant these devices is more extensive than the other models and carries more risks[40,41].

4.4.2 Active Middle Ear Implants

MEIs are indicated in patients with mild to severe SNHL, where the ABG is less than 10 dB, have stable hearing loss, and speech discrimination is more than 50%. They are also indicated in conductive or mixed hearing loss where bone conduction thresholds are stable and a healthy middle ear. The procedure is more complicated than BAHAs but they offer better speech in noise environment, sound localisation and a more natural sound quality[42].

The VSB (Med-El, Austria) like the Bonebridge (Med-El, Austria) has a magnetic connection between the microphone/external processor with the internal processor which is implanted onto the skull under the skin behind the ear. The electrical signals are channelled via an electrode to a floating transducer. The transducer can be placed onto the incus or to any fenestra and vibrates to create kinetic energy in the middle ear which is transmitted to the inner ear. Since the microphone is external and visible, this is a partially implanted device[42].

Unlike the VSB, the Carina (Cochlear, Australia) has all its components under the skin making it a completely implantable device. The microphone is subcutaneous and connected to the

signal processor which is embedded into the skull. The processor sends signals to the floating transducer. The benefit is it can be used even in water, which is preferred by swimmers, and can be charged magnetically[42].

The Codacs (Cochlear, Australia) MEI was designed for severe to profound mixed hearing loss up to 140dB. The main indication for this device is otosclerosis. It is partially implantable device with a magnetic connection. The internal processor/stimulator controls an actuator which is fixed within the middle ear and has an artificial incus which is coupled with a standard stapedotomy prosthesis[42].

4.4.3 Cochlear Implant

This is a partially implanted inner ear implant like the VSB. However, the electrode does not have a floating transducer, but is instead inserted via the round window directly into the cochlea, the organ that changes kinetic energy to electrical impulses. The electrode provides the electrical impulse to be sent to the brain via the nerves. It is reserved for patients with profound hearing loss (dead ear)[43].

Patients with advanced otosclerosis can have stapes surgery first and be fitted with hearing aids, or may have a combined surgery with MEI (with VSB the surgery is called “power stapes). If this is not successful, they can afterwards have a cochlear implant[44].

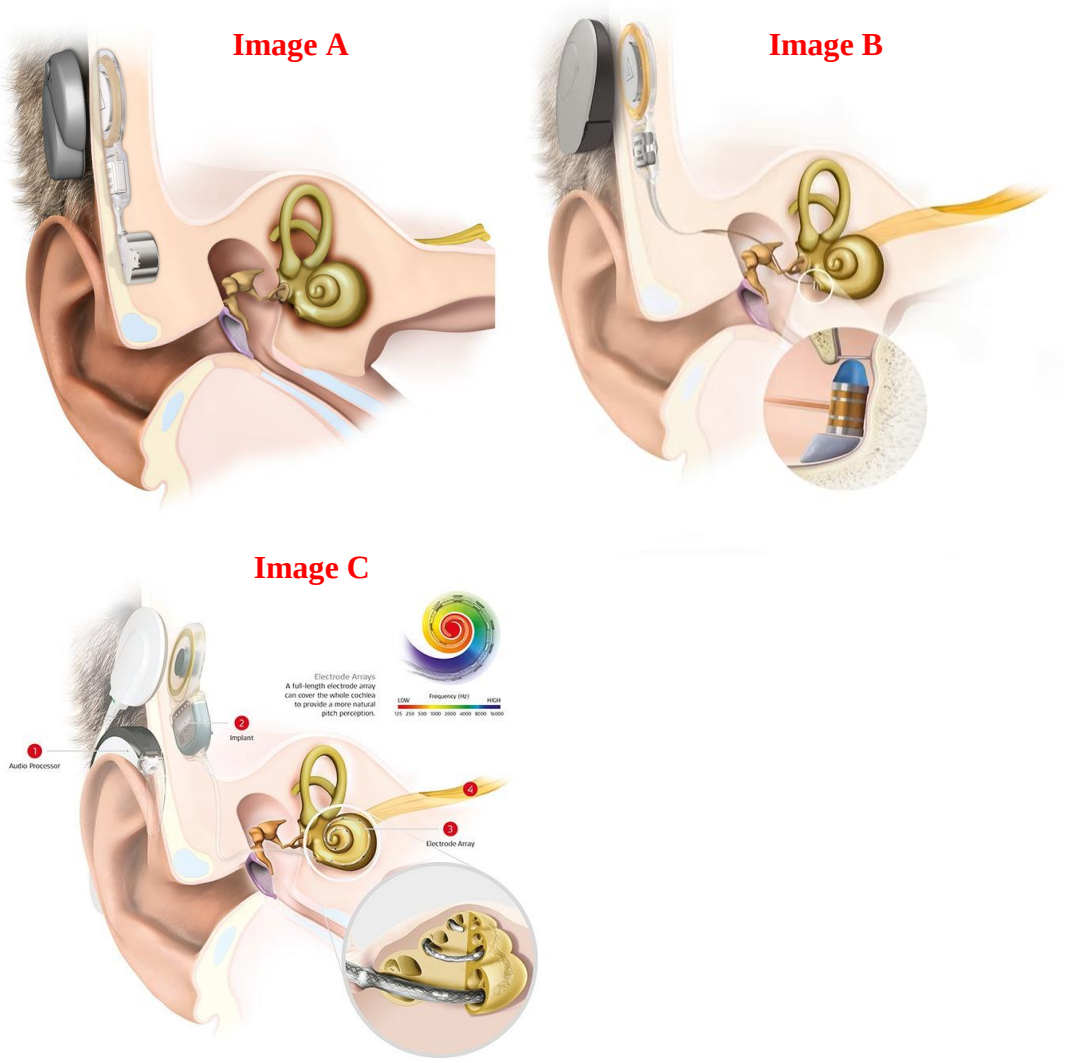


FIGURE 8: Image A: Bonebridge (Med-EL, Austria); Image B: Vibrant SoundBridge (Med-El, Austria) with a round window coupler; Image C: Cochlear implant (Med-El, Austria)[45].

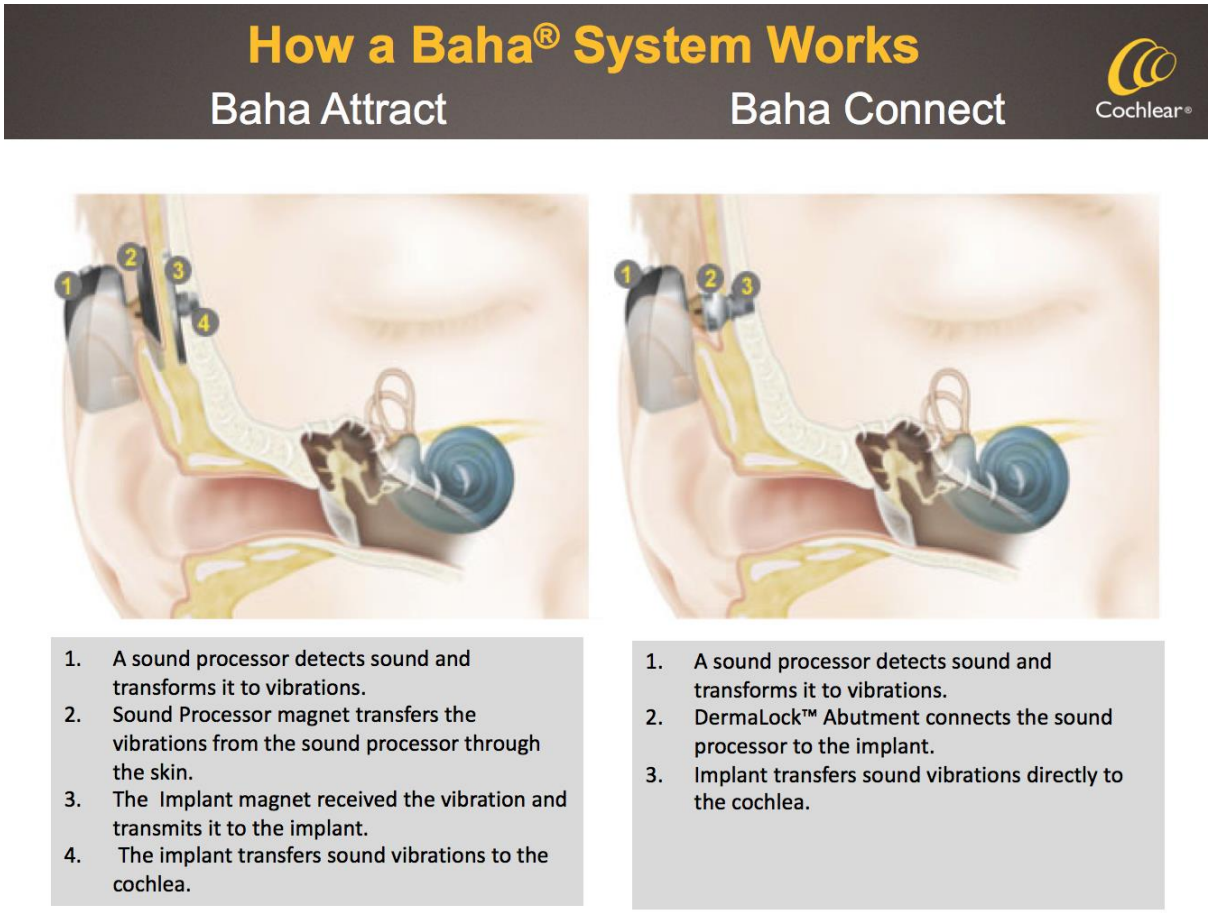


FIGURE 9: TOP: The BAHA Attract and BAHA Connect next to each other for comparison (Cochlear, Australia). BOTTOM: The Codacs MEI system (Cochlear, Australia)[46].

BTE – Behind the Ear, AI – Artificial Incus, MEI – Middle Ear Implant

5 OBJECTIVE

Innovation happens when something new is introduced to an established process with the aim to improve its effectiveness and/or its efficiency. Innovations in surgery happen constantly, improving the operating and patient experience while meeting, or even surpassing, previously established outcomes.

Since its discovery mid 19th century, the management of otosclerosis, a common cause of progressive hearing loss, has been primarily surgical and focused on the stapes.

However, there were several different techniques trialled before the current one was established, almost a century after its discovery. Even now and although the basic steps have not changed, technological and scientific progress continue to refine this already successful procedure.

The endoscopic approach and the NiTiBOND (Heinz Kurz, Dusslingen, Germany) stapes prosthesis are two such innovations in stapedotomy which is the final form of the surgical treatment for otosclerosis. The former adds a new point of view for the surgeon and threatens to dethrone the microscope as the main viewing tool for this type of surgery. The latter adds a small change to the shape of the ever-evolving prosthesis but whose effect might be long reaching.

Every innovation, to demonstrate its effectiveness and/or efficiency, needs to be validated by comparing it to the established conventional method. These studies help to inform the surgeon and the patient in choosing to undertake the surgical procedure whether to incorporate these innovations.

Our goal was to evaluate the endoscopic approach and the NiTiBOND (Heinz Kurz, Dusslingen, Germany) stapes prosthesis and provide the necessary information to help in their validation, and in their consideration for utilization in surgery. For this reason a meta-analysis and systematic review was performed on endoscopic versus microscopic stapes surgery outcomes and a comparison of intermediate-term hearing results of NiTiBOND and Nitinol prostheses in stapes surgery was demonstrated.

6 ENDOSCOPIC VS. MICROSCOPIC STAPES SURGERY OUTCOMES: A META-ANALYSIS AND SYSTEMATIC REVIEW

6.1 INTRODUCTION

The microscope is the conventional method used by the ear surgeons to view the middle ear structures, allowing for binocular vision and the freedom of both hands. Its main disadvantage is the need for an unobstructed, direct view of the operating area[47]. The endaural incision, drilling of the bony auditory canal, regular repositioning of the patient and of the surgeon are a few examples of how the operation has to adapt to the microscope. Nevertheless, the microscope has proven itself as the tool of choice in stapes surgery with reliable outcomes[48].

In contrast, the endoscope has only recently been introduced as an alternative viewing apparatus for middle ear surgery. Since its beginnings more than fifty years ago, it has become the modern way to visualize middle ear structures, gradually making its way into the surgical realm[49,50]. Initially, its use was limited as an adjuvant tool to improve detection in cholesteatoma surgery and in "endoscopically assisted" ear surgery[51-55]. Soon, surgeons realized that it can be used to replace the microscope entirely for certain operations such as stapes surgery with outcomes comparable to the microscopes[56]. The endoscope can offer a close-up view of the stapes footplate, with minimal drilling of the external auditory canal and reduced manipulation of the chorda tympani nerve[57-59]. The magnified, wide-field view and the improved illumination provide a safer manipulation of the stapes superstructure, the footplate, and the chorda tympani. In their study, Bennett et al. concluded that all the regions of the middle ear have a better visualization by the endoscope (0, 30 and 45 degree) compared to the microscope[60]. However, the endoscope is not without its drawbacks which include the loss of three-dimensional vision and the use of one hand, resulting in surgeons being reluctant to change from the microscope because of a possible long learning curve[47,61]. It has also been reported anecdotally that heat emanating from the light of the endoscope can also injure the chorda tympani nerve while the loss depth perception can impact the choice of prosthesis length and thus hearing outcomes. Irrigation is therefore paramount with both techniques.

Recently, there has been a number of publications comparing the two modalities and only one review, but no meta-analysis that attempted to collect all evidence on the field[62]. Therefore, we decided to systematically review the literature for studies that compared endoscopic with microscopic stapes surgery in order to perform a meta-analysis to test our hypothesis: endoscopy performs better than microscopy.

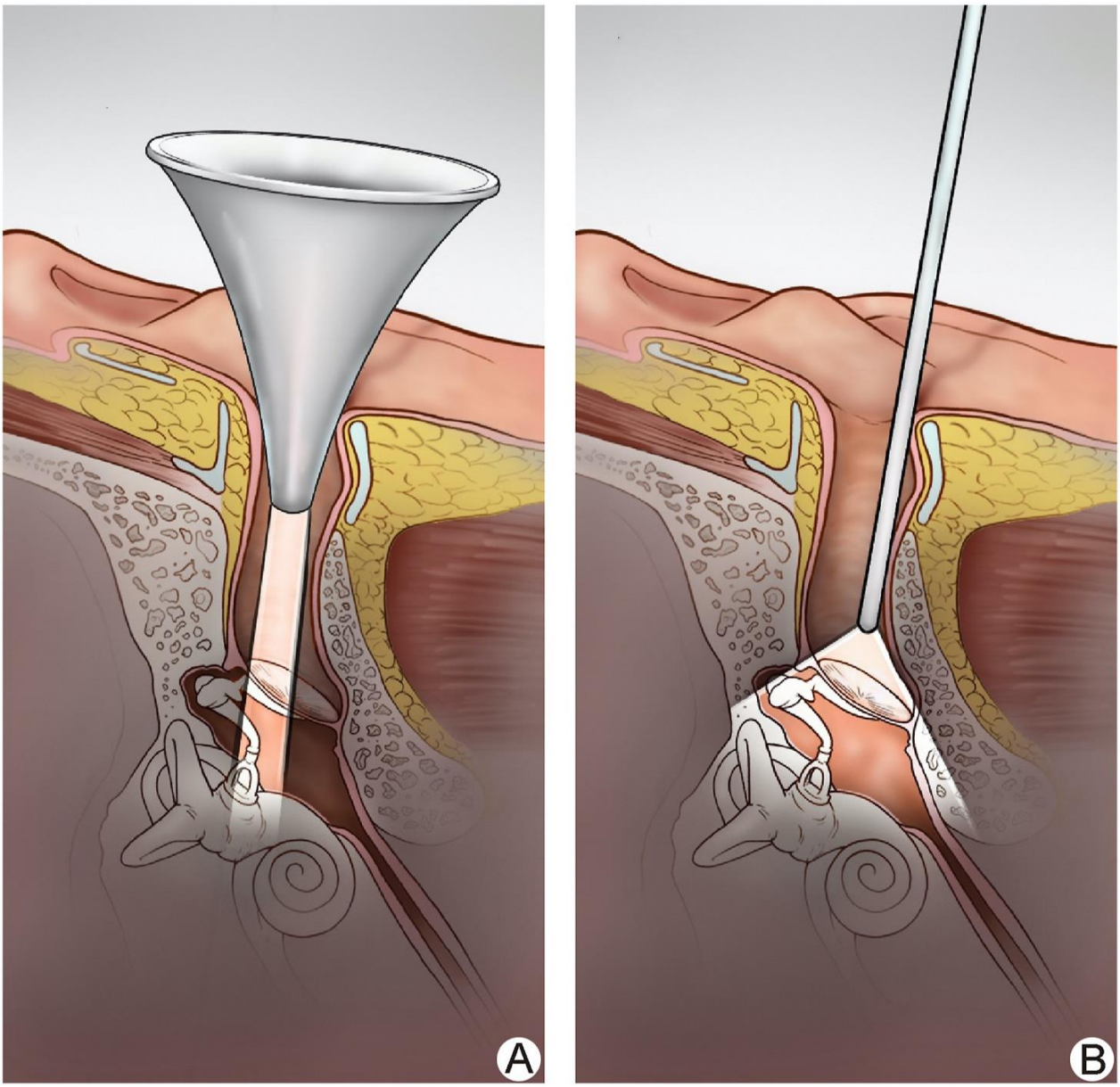


FIGURE 10: Anatomy illuminated by microscope versus endoscope. A: The size and shape of the external auditory canal and speculum limit the microscopic view. B: The endoscopic image is captured in close proximity to the surgical field with a wide-angle lens, overcoming many of the anatomic limitations of the microscope. Illustration courtesy of Brian Dunham and Eo Trueblood[63].

6.2 MATERIALS AND METHODS

This meta-analysis adheres to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[64] and was registered onto the PROSPERO under the registration number of CRD42018095617.

6.2.1 Search Query

A search was performed in the PubMed, Embase, Cochrane, Web of Science, Clinical Trials, WHO and Scopus databases from inception up to 6th June 2018. Our search query was the combination of free text terms and Medical Subject Headings, as follows: (endoscop* OR microscop* OR conventional OR traditional) AND (stapedotomy OR stapedectomy OR stapes OR otosclerosis). Cited and citing articles or relevant papers were hand searched to ensure the detection of all available records.

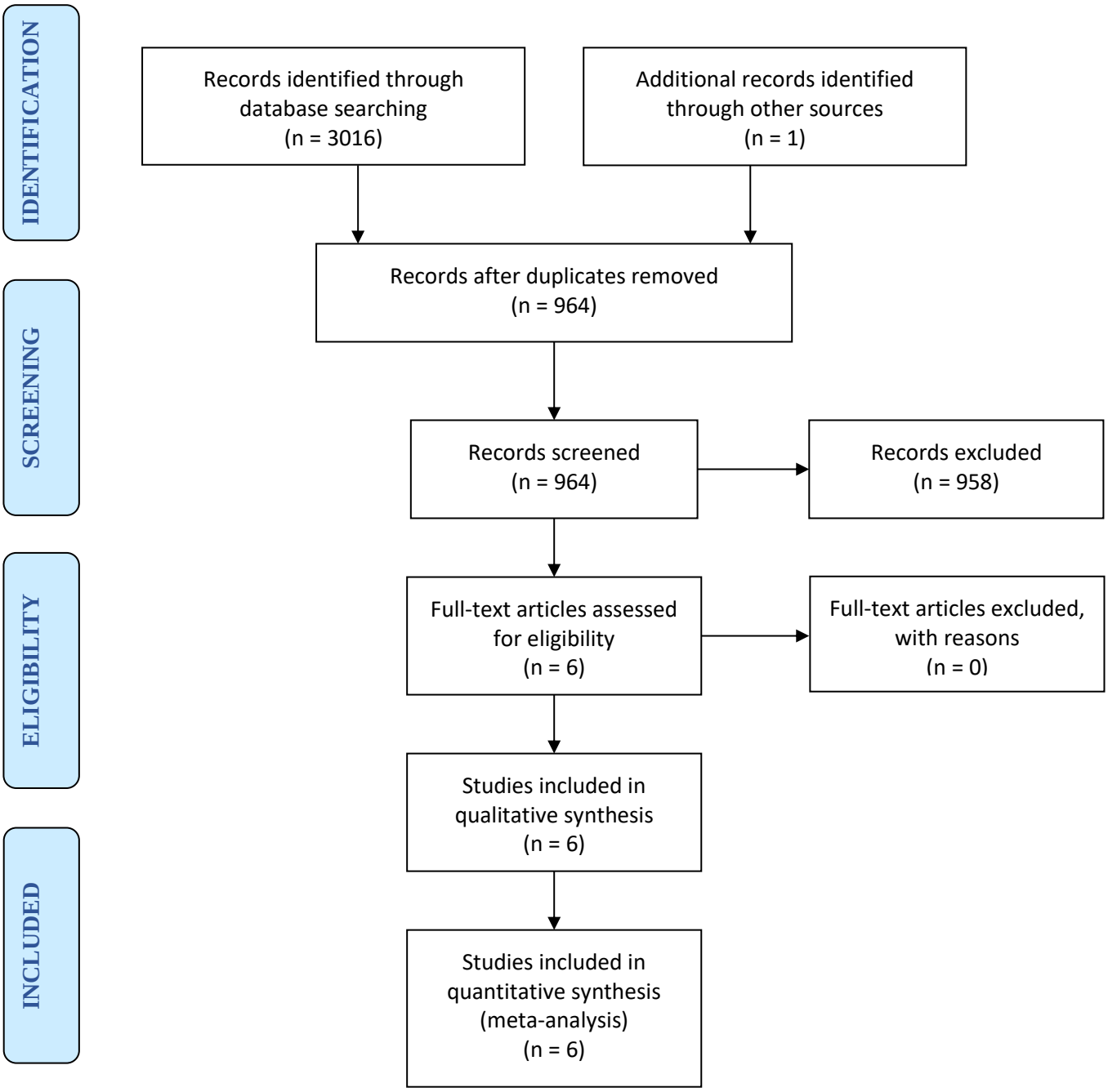
6.2.2 Selection and eligibility

Yield of search was compiled in a reference manager software (EndNote 7.4; Clarivate Analytics, Philadelphia,PA, USA) to remove overlaps between databases and duplicate records. Remaining records were selected by title, abstract, and full text by two review authors in duplicate (A.K. and I.T.). If an agreement could not be reached, the dispute was resolved with the help of a third investigator (P.R.). We chose studies whose population were patients suffering from conductive hearing loss due to stapes fixation and undergoing stapes surgery, which was carried out either with the endoscope or the microscope and recorded intraoperative and/or postoperative outcomes [65]. Only controlled studies were included. Primary outcomes were the average postoperative ABG and injury to the chorda tympani nerve. Secondary outcomes were the average operating times, intraoperative tympanic membrane perforation, and postoperative complications of taste disturbance, pain and dizziness. We searched for observational and experimental (randomized and non-randomized) controlled studies. Case reports, case series, letters, editorials, comments, and review articles were excluded, as well as conference abstracts.

6.2.3 Data Extraction

Our review team registered the collected data onto a predefined Excel (Microsoft, Redmond, WA) table. Two independent authors collected the data (A.K. and I.T.) and the table was reviewed by a third author (P.R.). We collected data for the primary outcomes and several secondary outcomes but only analyzed those reported by at least three studies.

FIGURE 11: Flow diagram of systematic review and meta-analysis



6.2.4 Study Quality Assessment

The quality of the studies was also independently assessed by the two authors (A.K. and I.T.) according to the Newcastle-Ottawa Scale (NOS) for cohorts, a validated quality assessment instrument for non-randomized trials, which consists of three domains of quality: selection, comparability, and exposure assessment[66]. Since bias cannot be described with numerical value, we graded each section as having an either high, low or uncertain level risk of bias. This was because the authors were uncertain of the risk of some of the elements found in each of the study methods. Any discrepancies were resolved through discussion. If an agreement could not be reached, the dispute was settled with the help of a third investigator (P.R.) and the senior statistician.

6.2.5 Statistical Analysis

Statistical analysis was performed by using Stata 11 SE (StataCorp, College Station, TX). We calculated pooled OR with 95% CI – in some cases by means of Peto method because of rare events – for dichotomous outcomes and WMD with 95% CI for continuous outcomes. The zero events were handled with continuity correction. We only considered results credible if they included three or more studies. We applied the random effect model with DerSimonian-Laird estimation. I^2 and χ^2 tests were used to quantify statistical heterogeneity and gain probability-values, respectively and were interpreted as per the "Identifying and measuring heterogeneity" section in the Cochrane handbook[67]. To check for publication bias, a visual inspection of funnel plots was performed. Sensitivity analysis was performed by omitting studies (one by one) from the analyses and recalculating to investigate the impact of the individual studies on the summary estimate.

6.3 RESULTS

The search yielded a total of 3017 articles. After excluding duplicates, we screened the remaining records for eligibility and found six articles for qualitative and quantitative synthesis[61,68-72]. The screening and selection process is depicted in figure 11. Characteristics of the included studies are presented in Table 1. All the six articles were non-randomized cohort studies with the exposure group being all patients who underwent fully endoscopic stapes surgery and the control group being all patients who underwent microscopic stapes surgery during the study period. A summary of our analysis results can be seen in Table 2 and the detailed forest plot and funnel graphs in Appendix A.

6.3.1 Primary Outcomes

6.3.1.1 Average Postoperative Air-Bone Gap

All studies evaluated average postoperative ABG but only five studies[61,68-70,72] performed the evaluation according to the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology – Head and Neck Surgery[73]. We analyzed the ABG in 3 groups. Group 1 was ABG of 10 dB or less. There was no significant difference (OR=1.80 [95% CI: 0.96 – 3.38]) and the I^2 and χ^2 statistical analysis suggested homogeneity ($I^2 = 0.0\%$, $p = 0.529$). When the Sproat et al. study was removed during sensitivity analysis, there was a statistically significant difference in favour of the endoscope[70]. Group 2 was ABG between 11 dB and 20 dB. There was no significant difference (OR= 1.49 [95% CI: 0.76 – 2.93]) the I^2 and χ^2 statistical analysis suggested homogeneity ($I^2 = 0.0\%$, $p = 0.753$). Group 3 was ABG > 20dB. Patients were more than two times likely to end up in this group if they were operated with the microscope (OR=2.51 [95% CI: 0.77 – 8.22]) but this was not statistically significant and the I^2 and χ^2 statistical analysis suggested homogeneity ($I^2 = 0.0\%$, $p = 0.673$).

6.3.1.2 Chorda Tympani Injury

Injury to the nerve was more than three times likely to happen with microscopic stapes surgery (OR=3.51 [95% CI: 1.55 – 7.93]) and was statistically significant. The I^2 and χ^2 statistical analysis suggested homogeneity ($I^2 = 0.0\%$, $p = 0.924$). During sensitivity analysis, if the Surmelioglu et al. study was excluded then there was no statistically significant difference[71].

6.3.2 Secondary Outcomes

6.3.2.1 Postoperative Taste Disturbance

Four studies evaluated postoperative taste disturbance which was more than two times likely to happen with microscopic stapes surgery (OR=2.36 [95% CI: 1.01 – 5.51]) and was

statistically significant[61,68,70,71]. The I^2 and χ^2 statistical analysis suggested mild heterogeneity (I^2 = 21.2%, p = 0.283).

6.3.2.2 Average Operating Time

Five studies[61,68,69,71,72] compared the average operating time but only three were included in meta-analysis due to insufficient published data[61,71,72]. Our results showed no significant difference between the two operations (WMD = 0.14 [95% CI, -11.69 – 11.98]). The results of the I^2 and χ^2 statistics suggested considerable heterogeneity (I^2 = 82.8%, p = 0.003).

6.3.2.3 Tympanic Membrane Perforation

Four studies[68,70-72] evaluated tympanic membrane perforation. Tympanic membrane perforation was not significantly different between the endoscopic and microscopic approach (OR=1.70 [95% CI: 0.44 – 6.58]). The I^2 and χ^2 statistical analysis suggested homogeneity (I^2 = 0.0%, p = 0.983).

6.3.2.4 Postoperative Pain

Four studies[61,69,71,72] evaluated postoperative pain which was the same for microscopic and endoscopic stapes surgery (OR= 0.84 [95% CI: 0.36 – 1.96]). The I^2 and χ^2 statistical analysis suggested significant heterogeneity (I^2 = 64.2%, p = 0.039).

6.3.2.5 Postoperative Dizziness

All studies evaluated postoperative dizziness and there was no statistical difference (OR=2.15 [95% CI: 0.94 – 4.89]). The I^2 and χ^2 statistical analysis suggested mild heterogeneity (I^2 = 0.0%, p = 0.49). Postoperative dizziness is significantly higher with microscopic stapes surgery when the Iannella study is removed for sensitivity analysis[61].

TABLE 1: CHARACTERISTICS OF INCLUDED STUDIES						
Main author and year	**Study Design**	**Number of ears**		**Outcomes**	**Follow-up time**	**Anaesthesia**
		Endoscope	**Microscope**			
Kojima et al 2013	Retrospective Cohort	15	41	Operation time, Post operation ABG, Dizziness, TM Perforation, Taste	6 to 12 months	General
Iannella et al 2016	Retrospective Cohort	20	20	Operation time, Post operation ABG, Chorda Injury	6 to 15 months	General
Daneshi et al 2016	Retrospective Cohort	19	15	Post-operative satisfaction, Post-operation ABG, Operation time, facial nerve paralysis, Chorda injury, Dizziness, Posterior canal removal	1 to 15 months	General
Surmelioglu et al 2017	Retrospective Cohort	22	24	Operation time, Post operation ABG, Dizziness, Chorda injury, TM Perforation	6 months	Local
Plodpai et al 2017	Retrospective Cohort	18	19	Operation time, Post operation ABG, Dizziness, Chorda Injury, TM Perforation	6 months	Local
Sproat et al 2017	Retrospective Cohort	34	47	Post operation ABG, Corda Injury, Dizziness, TM Perforation, Taste	Recorded first follow-up only	General
Total Number of Ears		128	166	294		

TABLE 2: SUMMARY OF OR STATISTICAL ANALYSIS

Outcome	Number of studies included	Number of events / Total number of cases		Result analysed	95% Confidence Interval		I^2 (%)	χ^2	Statistically significant
		Endoscope	Microscope		Lower	Upper			
PRIMARY OUTCOMES									
Group 1: ABG = 0 - 10 dB	5	83 / 106	100 / 142	OR = 1.80	0.96	3.38	0	0.529	No
Group 2: ABG = 11 - 20 dB	5	20 / 106	33 / 142	OR = 1.49	0.76	2.93	0	0.753	No
Group 3: ABG = 21 - 30 dB	5	3 / 106	9 / 142	OR = 2.51	0.77	8.22	0	0.481	No
Chorda Tympani Injury	6	3 / 128	20 / 166	OR = 3.51	1.55	7.93	0	0.924	Yes
SECONDARY OUTCOMES									
Average operation time	3	Not applicable	Not applicable	WMD = 0.14	-11.69	11.98	82.8	0.003	No
Post-operative Dizziness	6	35 / 128	70 / 166	OR = 2.15	0.94	4.89	0.0	0.49	No
Post-operative Pain	4	63 / 91	95/ 132	OR = 0.84	0.36	1.96	64.2	0.039	No
Post-operative Taste disturbance	4	7 / 91	19 / 132	OR = 2.36	1.01	5.51	21.2	0.283	Yes
Tympanic Membrane Perforation	4	2/89	5 / 131	OR = 1.70	0.44	6.58	0.0	0.983	No

OR = Odds Ratio WMD = Weighted Mean Difference ABG = Air Bone Gap

6.4 RISK OF BIAS ANALYSIS

The risk of bias within individual studies is graphically represented in Table 3. Plodpai et al. and Surmelioglu et al. studies were judged to have a low risk of bias, Iannella and Magliulo and Daneshi and Jahandideh moderate, and Kojima et al. and Sproat et al. high risk.

The main reason for studies being assessed as high risk was not stating, explicitly, their sources and methods (e.g., the randomization process, patient selection, patient records, theatre logbooks, audiology database).

The selection process was of particular interest as none of the studies were blinded and surgeons might have chosen patients with 'ideal' ears for the endoscopic procedures, a major confounder, or overestimated their results. Some of the authors tried to mitigate this selection bias by stating there was randomization but did not describe the process.

An uncertain risk of bias in some studies was that patients for each group were selected from different time periods. This was due to the surgeons operating initially with the microscope before they changed to the endoscope and using the data collected during those two periods for comparison. The difference of the surgeon's skill level between the two techniques could be considered as a confounder that would have influenced the selection process as mentioned earlier. In addition, we judged that to include patients who had been operated in the past (revision surgeries), patients who were not followed-up for minimum of 6 months or to exclude patients lost to follow-up due to inadequate data were causes of high risk of bias.

Most importantly, there was no standardized way of reporting outcomes and statistical results which we judged to carry the highest risk of bias. This was especially true in the case of the chorda tympani injury and postoperative taste disturbance. All studies were able to comment on whether the nerve was "injured" but most of them did no grade the level injury which could range from mild manipulation to severing the nerve. Similarly, there was no clarification on the definition of taste disturbance or how it was measured and for how long. Only two studies mentioned that the disturbance was transient[61,71]. We recommend that future studies state if the nerve was manipulated or severed and avoid using the term injury. In addition, taste needs to be measured with a validated method and any changes after surgery be reviewed in follow-up, stating if it was transient or permanent. The correlation of nerve injury with taste disturbance also needs to be statistically analyzed as some of the studies indicated no correlation between the two.

With regards to ABG measurements, previous endoscopic and microscopic stapes surgery case series have demonstrated improvement in hearing by closure of the average ABG rather than just the average postoperative ABG[57,58,65]. Only Surmelioglu et al. had published their results in this manner which we believe it to be a more accurate way to demonstrate surgical effectiveness[71]. Hence, we recommend that in the future results are published both ways to assist analysis. Other than Iannella, no other study clarified how they measured their operation time which made assessment of this parameter extremely difficult[61]. Surgeries done under local anaesthesia took longer which is a confounding factor and we assume this was due to patient movement during the procedure[71,72]. All studies compared dizziness but only two attempted to quantify it with respect to the duration (number of days after surgery) [61,68]. Similarly, only two out four studies attempted to quantify pain with respect to severity and the need for medication[61,69].

TABLE 3: RISK OF BIAS ANALYSIS						
	Daneshi 2016	**Kojima 2013**	**Sproat 2017**	**Plodpai 2017**	**Iannella 2016**	**Surmelioglu 2017**
Representativeness of the study						
Selection of the non-exposed cohort						
Ascertainment of exposure						
Demonstration that outcome of interest was not present at start of the study						
Comparability of cohorts on the basis of the design or analysis controlled for confounders						
Assessment of outcome						
Was follow up long enough for outcomes to occur						
Adequacy of follow-up of cohorts						
= LOW RISK		= HIGH RISK		= Uncertain Risk		

6.5 DISCUSSION

The main advantage of the endoscope over the microscope is the better visualization of the middle ear structures, requiring less bone removal and chorda tympani nerve manipulation which is one cause of postoperative taste disturbance[61].

Our study had concluded that the hearing outcomes of the endoscopic approach are similar to those of the microscope. However, there would have been a statistical difference for ABG < 10 dB favouring the endoscope if we had not included the results of Sproat et al. in our analysis[70]. In that study they compared the outcomes from separate time periods. We have stated earlier that the surgeon's skill level with the endoscope might not be the same as with the microscope which in turn might have affected their outcomes. At the same time, Sproat et al. were the only ones to use an otology audit tool to collect data and have provided the largest number of cases for analysis. It could be inferred that the other studies overestimated their results in favour of the endoscope especially in the absence of blinding.

The chorda tympani can clearly be visualized during the procedure with either intervention, making easy for surgeons to include in their notes if it was injured, and in turn to include it in their study outcomes. However, the level of manipulation is not stated and thus the term is vague, just us the terms used for postoperative taste disturbance in the absence of a validated tool and follow up. Although our study has shown statistically significant difference in favor of the endoscope for both outcomes, this result must be taken in context with the significant level of bias calculated in our analysis. In the Surmelioglu at al. study, the microscopic intervention, which was performed by either of two surgeons, had a very high level of chorda tympani injury, compared to the endoscope which performed only by the most experienced of the two surgeons[71]. The surgeon's experience, a confounder, could have influenced the outcomes in this study. We find no statistical difference in the chorda tympani injury when we remove Surmelioglu et al. from our analysis.

Theoretically, endoscopically operated patients would suffer less with postoperative dizziness because of reduced manipulation of the stapes superstructure due to better visualization. Equally, they would have complaint less about postoperative pain due to less drilling of the external auditory canal. However, our study has shown that there was no statistical difference with either outcome. In experienced hands, tympanic membrane perforation number will be minimal no matter which approach is used.

The operating time was the most poorly measured and published outcome, and this reflects the retrospective nature of the studies. While there is no significant difference in our analysis, a significant heterogeneity is seen in our results.

It was mentioned several times in the literature that the endoscope allows views with minimal or even without the need of drilling the bone of the posterior canal. This outcome was only sufficiently recorded by two studies[61,69]. Future studies should record if the drilling was done and try to quantify it (e.g. minimal, moderate, and extensive). Also, there is anecdotal evidence that depending on the surgeon's dominant hand they would drill one side and not the other due to space constraints.

Learning curve was a particularly recurring theme. The Iannella study was able to plot a learning curve for endoscopic stapes surgery by analyzing the average operating times of a surgeon by groups of cases and by time intervals[61]. In the first 10 cases done with the endoscope, the average operation time was significantly slower than the last 10 cases. However, they found no statistical difference between the average surgical times for endoscopic and microscopic approaches in the last 4-month period of their 1-year study and in the last 10 out of 20 cases. This would suggest that the learning curve for the endoscope is 10 cases. This is much smaller than the 60 to 80 cases for conventional microscopic surgery as published by Yung[74]. Nonetheless, the learning curve has often been framed as the main cause for surgeons' reluctance to change to the endoscope due to probable longer operation time[47,68]. Although the evidence is weak and not an outcome of this study, we believe surgeons should not be afraid to operate with the endoscope as the learning curve is not long and outcomes are similar or better than the microscopes, even at the early stages.

6.6 STUDY LIMITATIONS

Our meta-analysis used non-randomized studies which were done retrospectively and contained significant bias which reduced its level of evidence. By including only articles that directly compared the two surgeries we have limited our data pool. This has resulted in a theoretical increased risk of publication bias which could not be assessed reliably using the symmetry of the funnel plot due to the low number of eligible studies. All funnel plots can be found in the supplementary section. The authors contemplated the use of indirect comparison especially as these can offer outcomes from a larger number of cases without great inconsistency from a direct comparison[75]. However, this would not have decreased the risk of bias as the main risk factors of randomization, selection and publication would still exist, and new confounding factors would be creep in.

6.7 CONCLUSION

Overall, our study indicates endoscopic and microscopic stapes surgery have similar audiological success, with some data suggesting a lower risk of chorda tympani injury and postoperative taste disturbance with the endoscope. However, we acknowledge the limitations of our study and would like to encourage prospective randomize controlled trials to validate our results.

6.7.1 Funding

The study was supported by the Economic Development and Innovation Operative Program Grant (GINOP 2.3.2-15-2016-00048) and by the Human Resources Development Operational Program Grant (EFOP-3.6.2-16-2017-00006) from the National Research, Development and Innovation Office.

7 COMPARING INTERMEDIATE-TERM HEARING RESULTS OF NITIBOND AND NITINOL PROSTHESES IN STAPES SURGERY

7.1 INTRODUCTION

Thermal shape-memory nickel-titanium alloy stapes prosthesis has been used for more than a decade now in stapedotomy with studies showing equal and sometimes superior hearing outcomes to older types[76]. Their main advantage is that they offer crimp-free coupling as opposed to manual-crimping, resulting in less damage to the incus[77]. The two different prostheses used in our study consisted of a piston made of pure-titanium and a loop made of nickel-titanium alloy (Figure 12). The attachment loop has a thermal shape memory and adopts the predefined shape when heat is applied[78]. The loop of the newer, structurally improved thermal-shape memory NiTiBOND (Heinz Kurz, Dusslingen, Germany) piston has a daisy shape, which results in reduced coverage of the surface of the long process of the incus when compared with the crosier-shaped SMart Nitinol piston (Olympus, Center Valley, Pennsylvania, USA). When closed, the Nitinol prosthesis covers almost two-thirds of the mucosal surface of the long process, while the NiTiBOND covers significantly less[78]. This leads to reduced mucosal strangulation as compared with the Nitinol and might theoretically lead to reduced incus necrosis. The NiTiBOND loop has four integrated contact zones, conforming to the asymmetrical dimensions of the incus. Additionally, the loop also features three independent activation zones which keep thermal transfer from the mucosa surface during laser activation. These activation zones can be sequentially closed producing a custom coupling to the individualized incus[79].

This study aimed to compare the intermediate-term hearing thresholds following the application of a self-crimping heat-memory NiTiBOND piston and a Nitinol piston[80]. We hypothesised that the NiTiBOND is superior to the Nitinol prosthesis in the intermediate-term.

7.2 MATERIALS AND METHODS

7.2.1 Study design

This is a retrospective cohort study, reported according to the STROBE Statement for cohort studies[81].

7.2.2 Ethical considerations

The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, University of Pécs, Hungary (approval number: 8338).

7.2.3 Population, interventions and outcomes

We reviewed our records for all patients who underwent stapedotomy with either the NiTiBOND or Nitinol prosthesis in the Department of Otorhinolaryngology-Head and Neck Surgery, Medical School, University of Pécs (Pécs, Hungary). Only primary cases were included, and patients with chronic ear diseases, with revision surgeries or who did not return for their annual hearing tests were excluded from the study.

The prosthesis used measured 4.5 – 4.75 x 0.6 mm, following the measurement of the distance between the oval window and the lateral surface of the long process of the incus. The surgical technique was identical with the exception of the prosthesis. The NiTiBOND prostheses were implanted between September 2012 and September 2017, and the Nitinol prostheses were applied between November 2005 and January 2007.

It is our standard protocol as part of our stapedotomy procedure for patients to have yearly hearing evaluations. The hearing values were recorded as per the guidelines of the American Academy of Otolaryngology[73]. Besides the baseline values, results from the most recent hearing assessments were collected. Our primary outcome was clinical success defined as a postoperative ABG <10 dB at follow-up.

7.2.4 Statistical analysis

When we treated hearing results as continuous variables, the Mann-Whitney U test and the Wilcoxon Signed Rank test were used for univariate analysis and $p < 0.05$ was considered to be statistically significant. We calculated the statistical difference between the pre- and post-operative values in the NiTiBOND group (p1), the statistical difference between the pre- and postoperative values in the Nitinol group (p2), the statistical difference between the two groups' preoperative values (p3) and the statistical difference between the two groups' the postoperative values (p4).

When we treated hearing results as dichotomous variables (success vs. failure, as defined by a post-operative ABG cut-off of less than 10 dB), we performed binary logistic regression (with the logit link function and without model selection) and calculated OR with the Wald 95% CI. After univariate analysis, we performed multivariate analysis where, in addition to the type of implant, models one and two included two (age and sex) and four explanatory variables (age, sex, length of follow-up and preoperative bone conduction), respectively. The convergence criterion was satisfied in both models. No values were missing (91 participants in both groups).

FIGURE 12: The two different types of prostheses. Nitinol (A) and NiTiBOND (B)[79]

7.3 RESULTS AND ANALYSIS

Altogether, 91 patients were eligible for inclusion in our study. The NiTiBOND group had 53 patients (with an average 4.1 of years of follow-up) and the Nitinol had 38 (with an average 4.4 of years of follow-up). Female predominance was observed (40 females out of 53 patients in the NiTiBOND group, and 30 out of 38 in the Nitinol group). The patients' mean age was 44.5 years (range, 22–68 years) in the NiTiBOND group and 40.4 years (range, 27–69 years) in the Nitinol group.

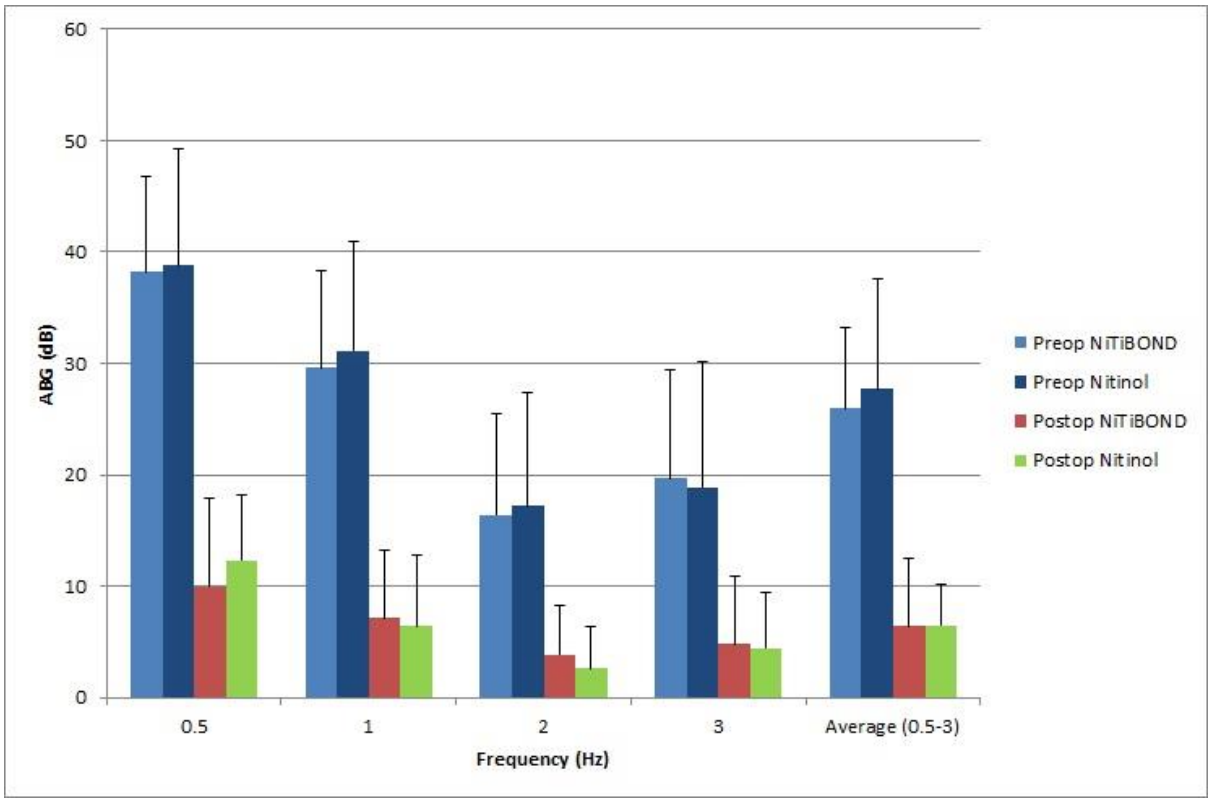


FIGURE 13: NiTiBOND mid-term (4.1-years) and Nitinol mid-term (4.4-years) postoperative hearing results as compared with the merged preoperative mean air-bone gap (ABG) measures. Bars indicate 1 Standard Deviation.

Table 4 summarises the comparison between pre- and postoperative hearing values within the NiTBOND and the Nitinol groups, while Table 5 summarises the same values between the groups. The difference between the pre- and post-operative mean ABGs, as presented in Figure 13, was statistically significant within both groups confirming the hearing improvement with both prostheses. Bone conduction similar pre and post operation within each group, indicating no worsening of sensoneural hearing due to the procedure. Air conduction statistically different within each group, indicating improvement of conductive hearing after the procedure. However, there was no statistically significant difference when ABGs from the two groups were compared with each other.

All patients achieved a postoperative ABG <20 dB, except 1 patient in the NiTiBOND group (ABG= 28 dB; pre- vs post-operative ABG, p = 0.397). Clinical success (defined as an ABG of 10 dB or less) was achieved in 83 % and 86 % of cases in the NiTiBOND and Nitinol groups, respectively, with no significant difference between groups (OR = 0.74, 95 % CI = 0.23–2.42, p = 0.620 for univariate analysis). The results were consistent after adjustment for co-variates for model one (OR = 0.72, 95 % CI = 0.21–2.39, p = 0.586) and for model two (OR = 0.78, 95 % CI = 0.21–2.93, p = 0.716), as summarised in Table 6).

No cases of sensorineural hearing loss occurred following surgery. To date, we have observed one transient facial paralysis with NiTiBOND piston and 1 with Nitinol but both patients have subsequently recovered completely.

TABLE 4: INTRAGROUP STATISTICAL ANALYSIS						
Variables	NiTiBOND		p1	Nitinol		p2
	Preoperative	Postoperative		Preoperative	Postoperative	
Mean ABG	25.9 ± 7.2	6.46 ± 5	< 0.001*	27.7 ± 9.8	6.48 ± 3.6	< 0.001*
Mean BC	29.2 ± 9.9	27.5 ± 14.1	0.076	22.7 ± 7.7	20.4 ± 8.1	0.129
Mean AC	55.2 ± 12.5	33.9 ± 16.7	< 0.001*	50.4 ± 14	26.9 ± 7.6	< 0.001*
Mean BC (1,2 and 4 kHz)	29.9 ± 10.7	30.2 ± 15.5	0.639	23.6 ± 9.5	21.9 ± 8.9	0.495
AC at 4 kHz	55.5 ± 20.3	44.1 ± 21	< 0.001*	48 ± 21.1	35 ± 13.7	< 0.001*

ABG = Air-Bone Gap, BC = Bone conduction, AC = Air conduction, SD = standard deviation, * = significant difference.

TABLE 5: INTERGROUP STATISTICAL ANALYSIS						
Variables	Preoperative		p3	Postoperative		p4
	NiTiBOND	Nitinol		NiTiBOND	Nitinol	
Mean ABG	25.9 ± 7.2	27.7 ± 9.8	0.631	6.46 ± 5	6.48 ± 3.6	0.647
Mean BC	29.2 ± 9.9	22.7 ± 7.7	< 0.001*	27.5 ± 14.1	20.4 ± 8.1	0.005*
Mean AC	55.2 ± 12.5	50.4 ± 14	0.043*	33.9 ± 16.7	26.9 ± 7.6	0.041*
Mean BC (1,2 and 4 kHz)	29.9 ± 10.7	23.6 ± 9.5	0.001*	30.2 ± 15.5	21.9 ± 8.9	0.01*
AC at 4 kHz	55.5 ± 20.3	48 ± 21.1	0.03*	44.1 ± 21	35 ± 13.7	0.058

ABG = Air-Bone Gap, BC = Bone conduction, AC = Air conduction, SD = standard deviation, * = significant difference

TABLE 6: PREDICTORS OF AN ABG 10 dB OR LESS AT FOLLOW-UP

Parameters	Model 1*			Model 2**		
	Beta	Odds ratio (95% CI)	P-value	Beta	Odds ratio (95% CI)	P-value
Implant (Nitinol vs NiTiBOND)	-0.3359	0.72 (0.21-2.39)	0.586	-0.2452	0.78 (0.21-2.93)	0.716
Sex (male vs female)	-0.0236	0.98 (0.24-4.01)	0.974	-0.0411	0.96 (0.23-3.96)	0.955
Age at operation (years)	-0.0512	0.95 (0.90-1.01)	0.074	-0.0436	0.96 (0.90-1.02)	0.171
Follow-up duration (years)	-	-	-	0.1745	1.19 (0.68-2.09)	0.544
Mean pre-operative BC threshold	-	-	-	-0.0086	0.99 (0.93-1.06)	0.810

Type of implant and sex were used as dichotomous variable; age at operation, length of follow-up and mean pre-operative bone conduction threshold were used as continuous variables (unit shown in brackets in the first column). BC = Bone conduction, CI = Confidence Interval

*adjusted for age at operation and sex.

**adjusted for age at operation, sex, length of follow-up and mean pre-operative bone conduction threshold.

7.5 DISCUSSION

Our paper compares the audiological results of Nitinol versus NiTiBOND prostheses with the longest follow-up period to date. It has shown comparable audiological outcomes at an average of 4.1 and 4.4 years post-operatively for NiTiBOND and Nitinol, respectively. The authors demonstrated similar audiological outcomes in the short term when comparing the prostheses in 2016[82]. However, much larger patient cohorts are needed for an evaluation of long-term prosthesis stability. No suspicion of incus erosion or prosthesis luxation arose in the Nitinol group, but 1 patient developed a greater ABG postoperatively in the NiTiBOND group, which was still being investigated.

Other long-term follow-up studies published in the literature include an investigation by Green and McElveen. This study had a larger cohort, and ABG closures of less than 10 dB in 83.7 % of patients at 13.6 months post-operatively, with the use of a NiTiBOND piston[83]. Roosli and Huber reported ABG closures of less than 10 dB in 84.5% of patients at 12 months postoperatively with a Nitinol piston[84]. The intermediate-term postoperative mean ABG less than 10 dB achieved with the NiTiBOND piston in our study is similar to those reported by both the Roosli and Huber[84], and Green and McElveen[83] studies.

The ratio of postoperative ABG closure achieved was comparable with the data demonstrated by other authors reporting intermediate- or long-term results following the implantation of Nitinol prosthesis. Heywood et al. reported a 9.5-year postoperative ABG of 9.7 dB in their study consisting of 56 patients following stapedectomies with the application of Nitinol piston[85]. Lavy and Khalil reported a five year post-operative ABG of 5.89 dB among 48 patients with the use of Nitinol pistons[86]. Rajan et al. demonstrated a two-year postoperative ABG of 5.15 dB in their study consisting of 90 patients following the use of Nitinol prosthesis[87].

Wegner et al. published a systematic review of the effect of crimping techniques in stapes surgery in 2016[77]. They demonstrated superior hearing outcome in case of heat-crimping over manual or no crimping, although the longest follow-up period reported was two years among the studies included. Both prostheses are MR-compatible with 1.5 Tesla; no change was earlier demonstrated in either the position or the conformation of the Nitinol piston[88,89]. The pure nickel content of both prostheses is not likely to be accessible, as the surface of the nickel-titanium alloy is covered by titanium oxide after oxygen exposure[90,91].

The authors feel that the intraoperative manoeuvrability of NiTiBOND pistons is superior to the Nitinol. The daisy shaped NiTiBOND piston is wider and cornered due to the loops constructed in the head of the prosthesis, thus resulting in easier gripping and positioning of the piston as compared with the Nitinol. This is something not advertised on the manufacture's website, and which needs to be further evaluated with other centres publishing their data and opinions on this matter.

7.6 STUDY LIMITATIONS

The quality of evidence is limited by the study design (retrospective cohort study and case selection criteria). In addition, since the number of cases not achieving success was low in multivariate analysis (n=14), adjusted results of Model 2 may be underpowered.

7.7 CONCLUSION

Our study has shown similar hearing outcomes after 4 years rejecting our null hypothesis. However, the latest NiTiBOND stapes prosthesis offers significant structural innovations when compared to the Nitinol prosthesis, making its intraoperatively manoeuvrability easier.

8 NOVEL FINDINGS

Our two studies succeeded in their aim to provide the scientific and medical community with additional, more robust information on whether these two new innovations in stapes surgery can be considered as effective as their conventional counterparts. Furthermore, our research has found deficiencies in the methodology of studies and gaps in knowledge that lead to new research goals.

8.1 THE ENDOSCOPIC APPROACH VS THE MICROSCOPE

We were the first to pool the data of several studies and to improve the strength of their results when comparing the two methods. This has allowed us to confirm or reject the findings of each individual study, which sometimes contradicted each other and caused confusion. In addition, we have given gravitas to the validity of any positive findings.

Our evidence supports and re-enforces the findings that endoscopic surgery hearing outcomes are similar to the microscope, and therefore confirms the endoscope as a valid alternative. In addition, our evidence has confirmed the main benefit of the endoscope is its ability to look past structures that would otherwise obstruct view of the microscope. This allowed less manipulation of the chorda tympani nerve resulting in fewer nerve injuries and taste disturbances and would be preferable in cases where the opposite nerve has been damaged due to illness or surgery in the past.

We cannot support with our evidence that endoscopic surgery would cause less dizziness, pain or tympanic membrane perforations. Unfortunately, we could not answer the question of which surgery was quicker as the evidence was not sufficient. Similarly, we could not verify that endoscopic surgery requires less bone removal although this is another one of its advantages.

New research goals: The operating time and hospital stay are very important factors in both surgical and patient experience as well as for hospital costs. They need to be evaluated as microscopic approach stapedectomy or stapedotomy by certain surgeons can be done with patient awake, completed under 30 minutes and same day discharge. Can the endoscopic approach be performed the same way?

8.2 NITINOL VS NITIBOND STAPES PROSTHESIS

We are the first to have provided evidence of intermediate-term hearing level outcomes for both prostheses and to compare those outcomes. Our evidence supports that over 4 years both

prostheses perform similarly, validating the use of the NiTiBOND as an alternative. Hearing has not been reduced within those years which could indicate that:

- There is no displacement of the prostheses
- There is no incus necrosis
- The disease (otosclerosis) has not affected the prostheses

On reflection, imaging might have provided further information on the above deductions. However, this would require ethical approval as justification for CT, which is the preferred modality, carries significant radiation exposure. It is a research goal worth exploring.

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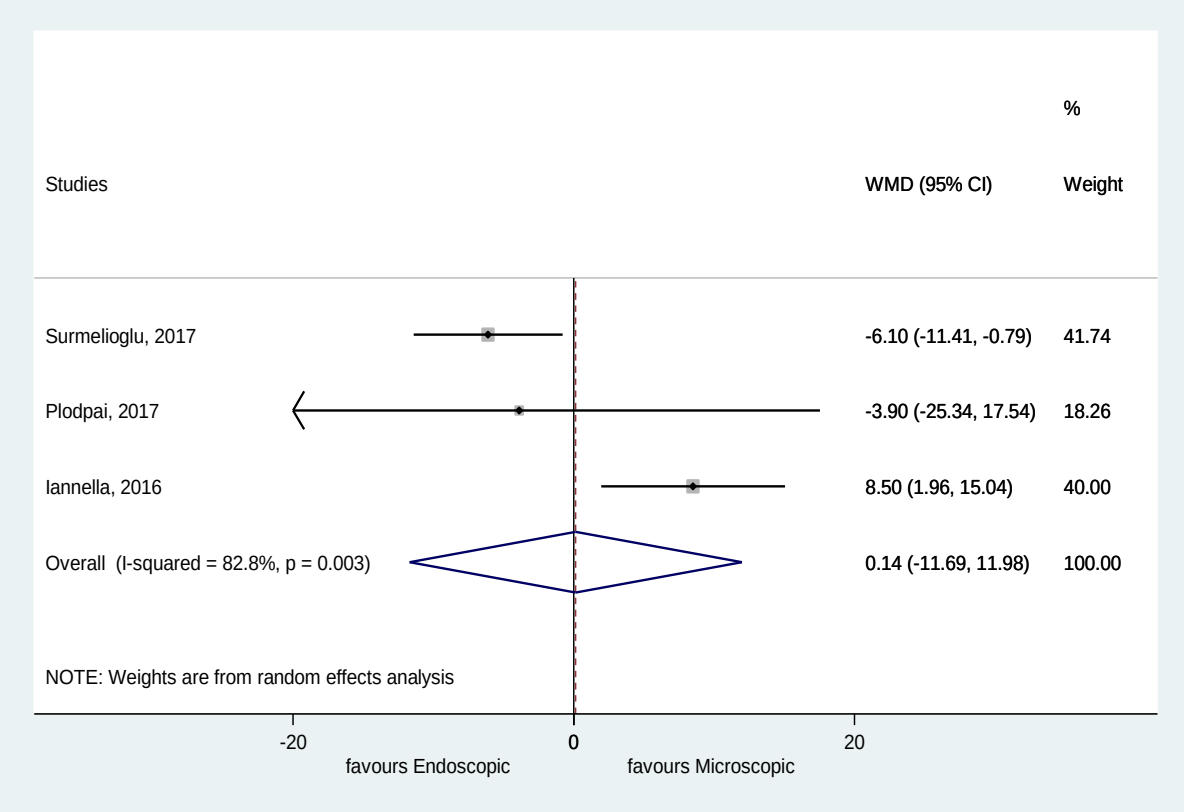
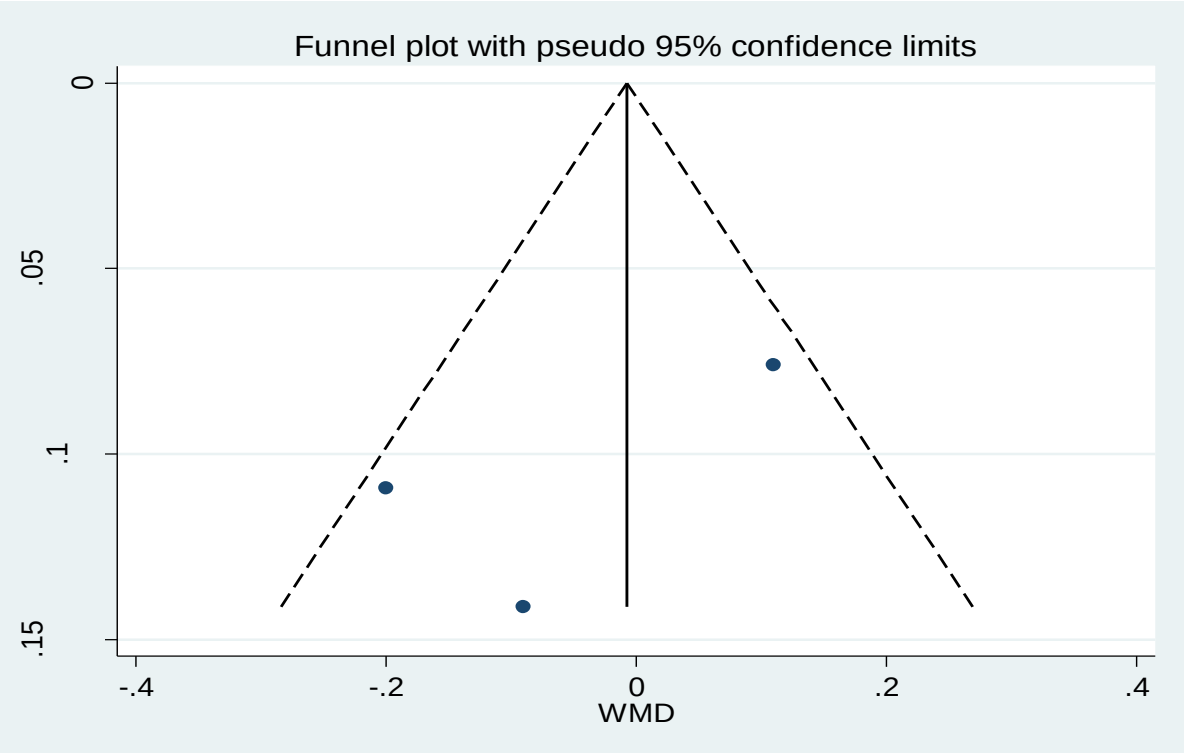
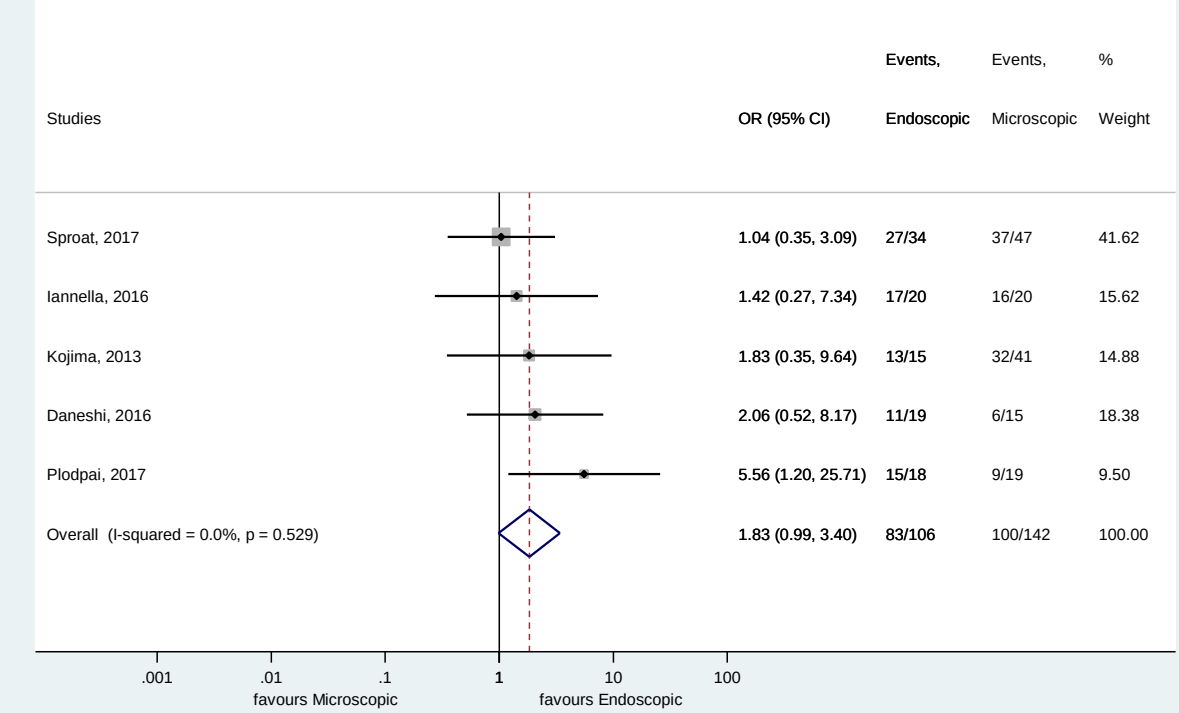
11 APPENDIX A: FORREST PLOT AND FUNNEL GRAPHS FOR STATISTICAL ANALYSIS OF ENDOSCOPIC VS MICROSCOPIC STAPES SURGERY

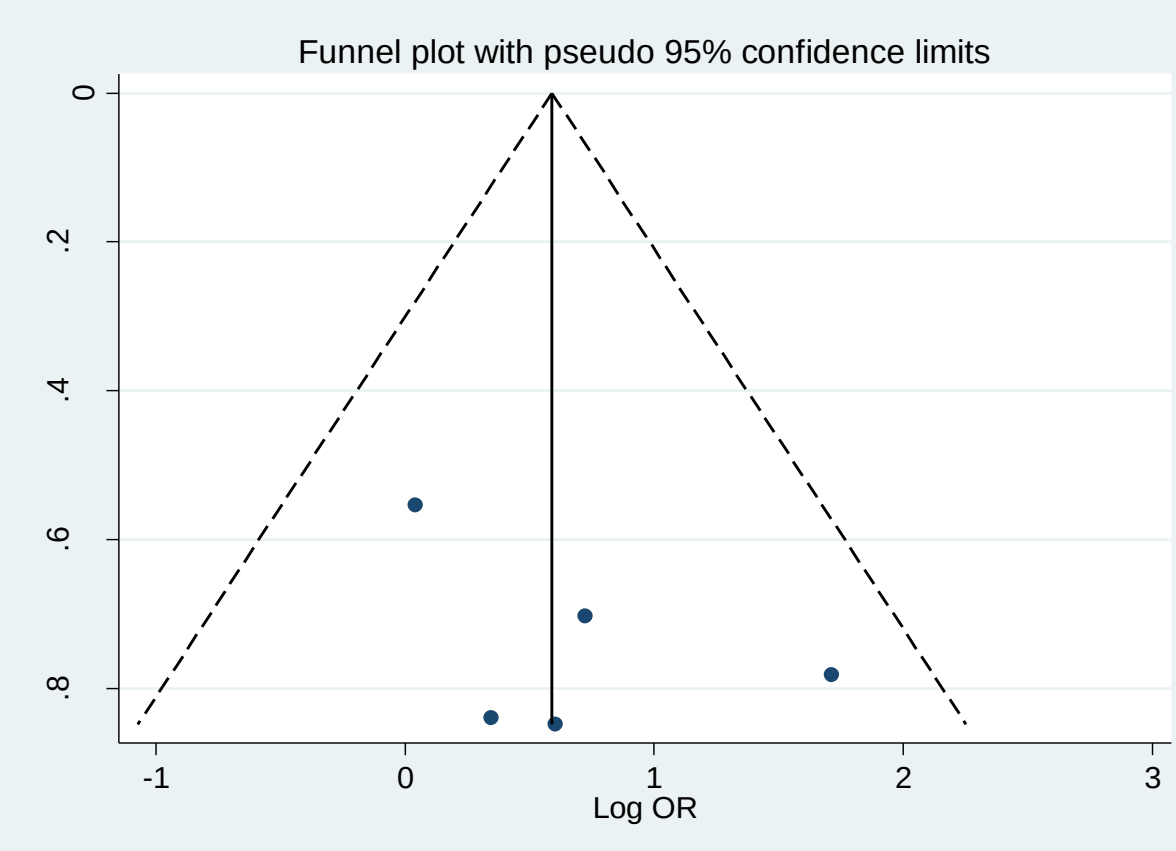
AVERAGE OPERATING TIME





AVERAGE POST-OPERATIVE ABG GROUP 1





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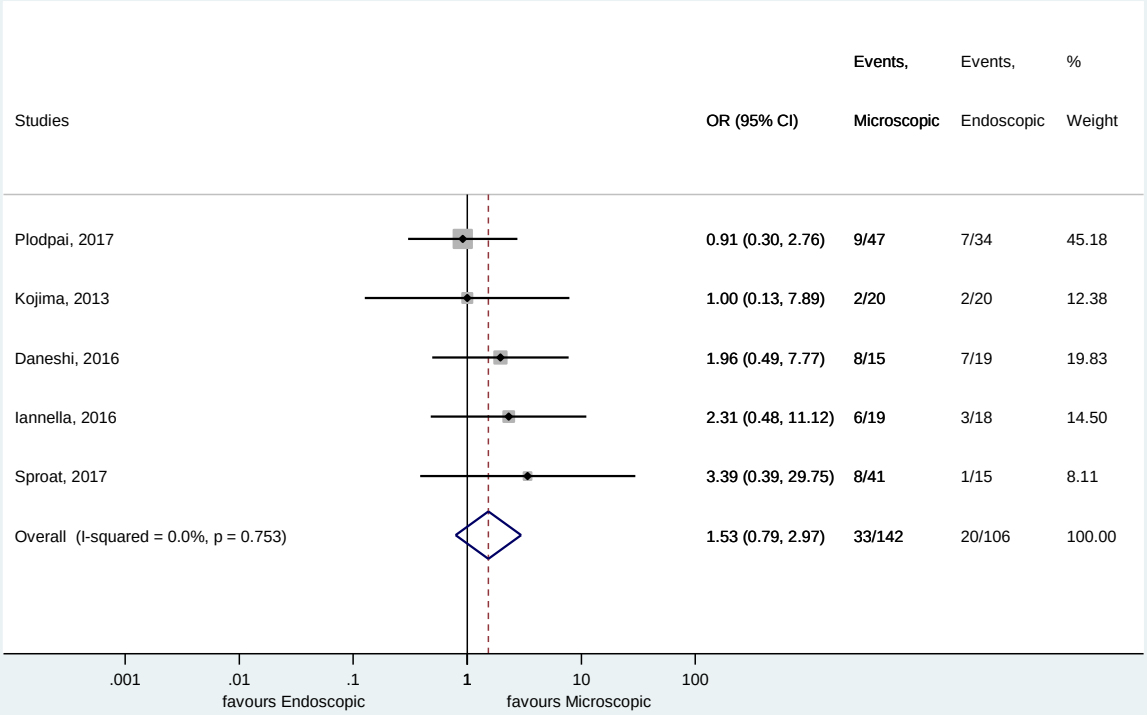

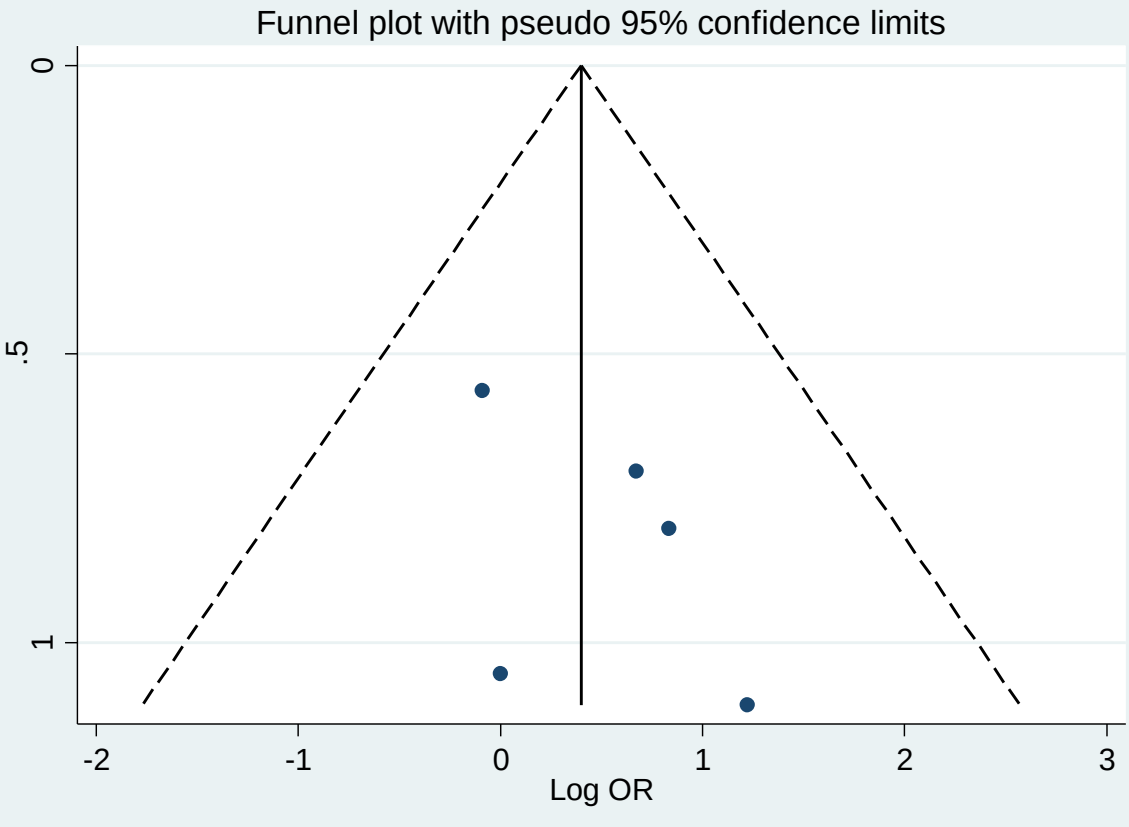

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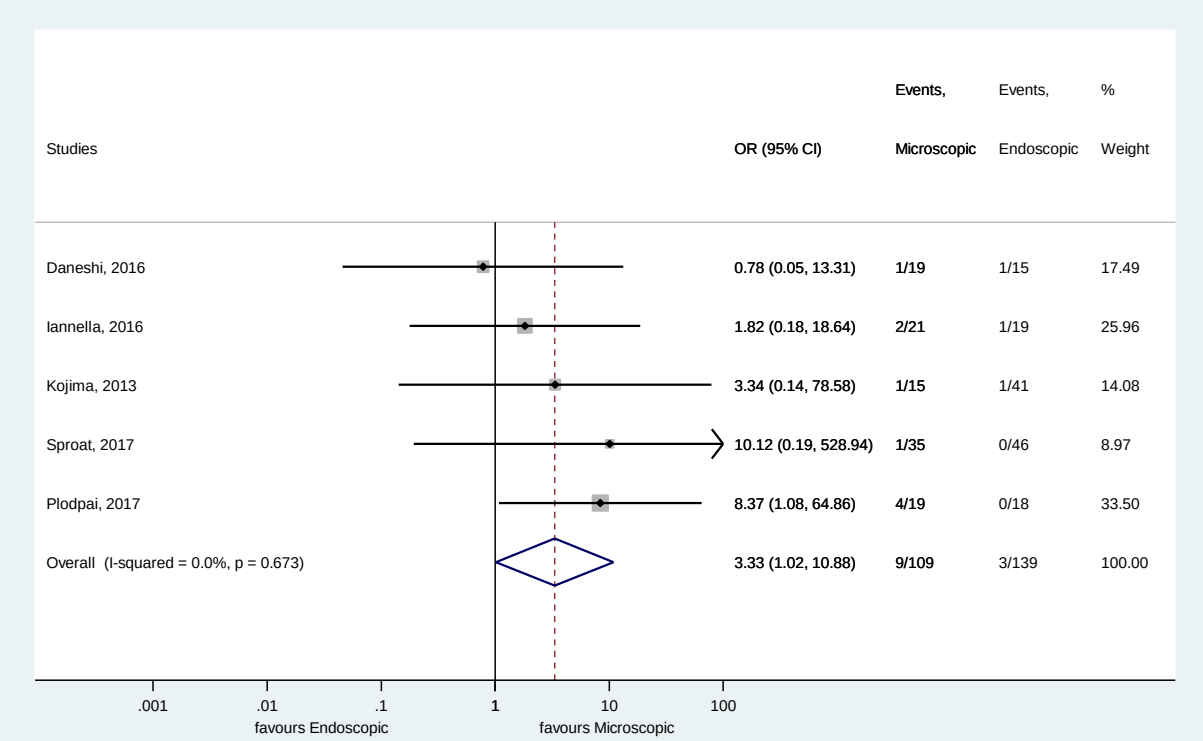
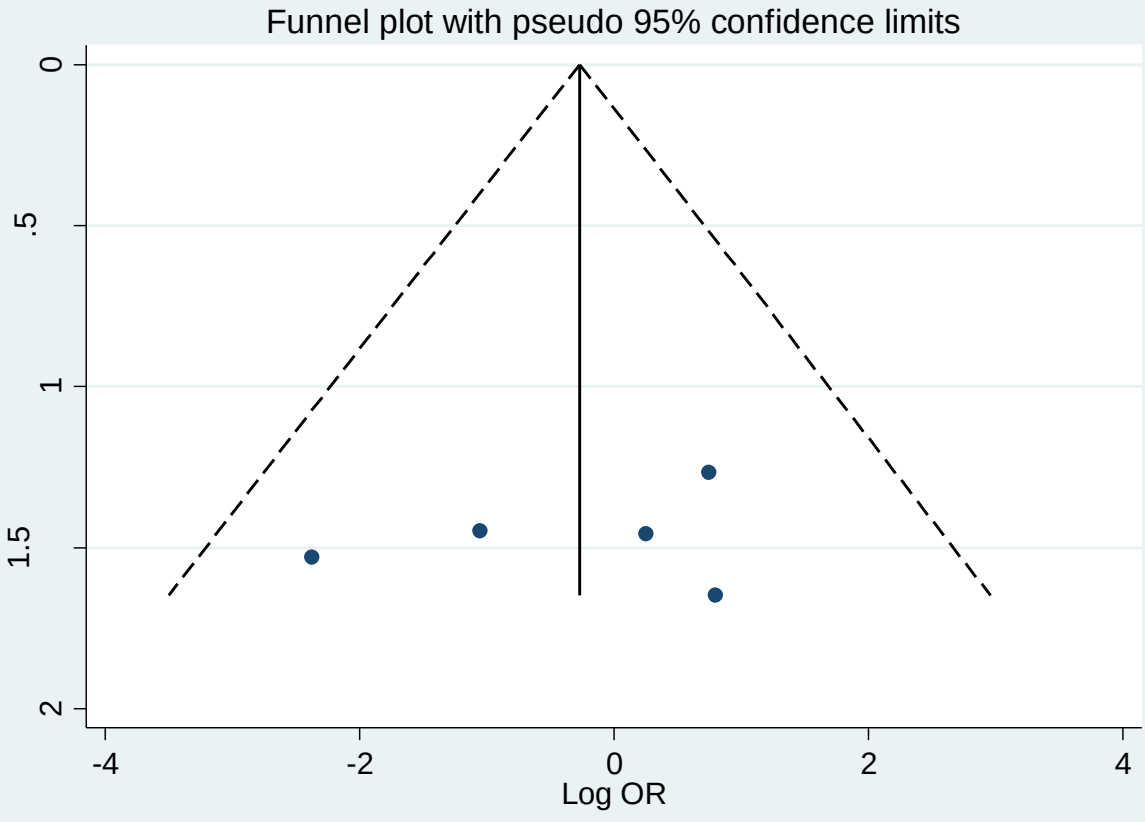
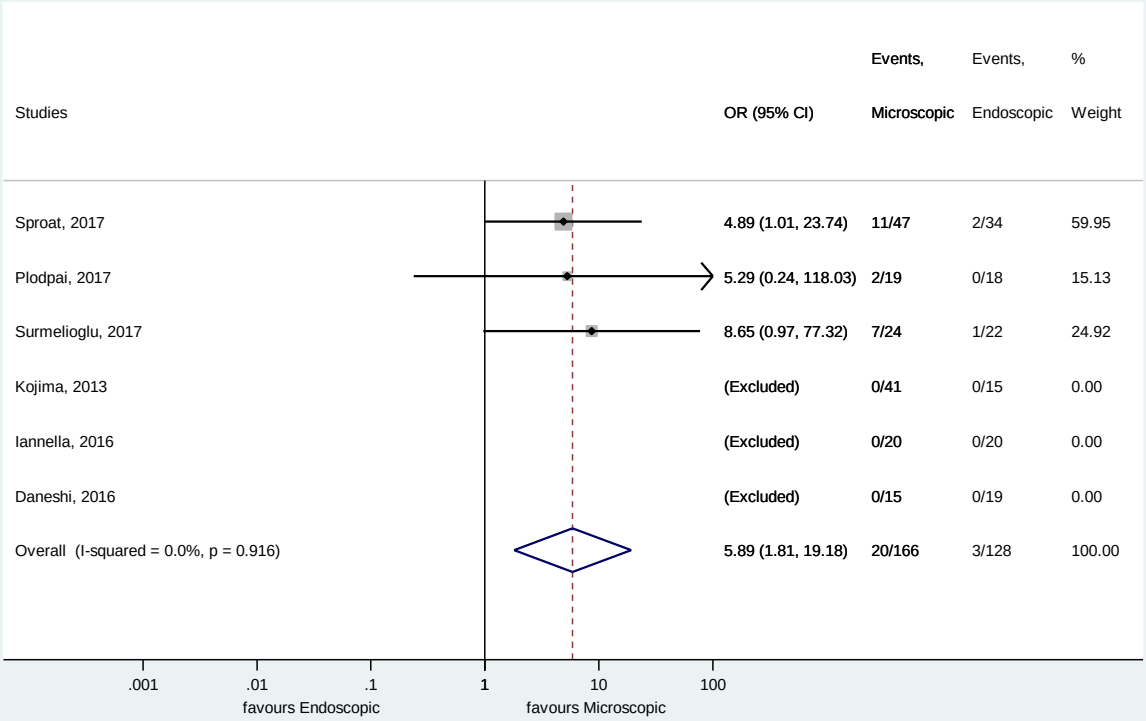
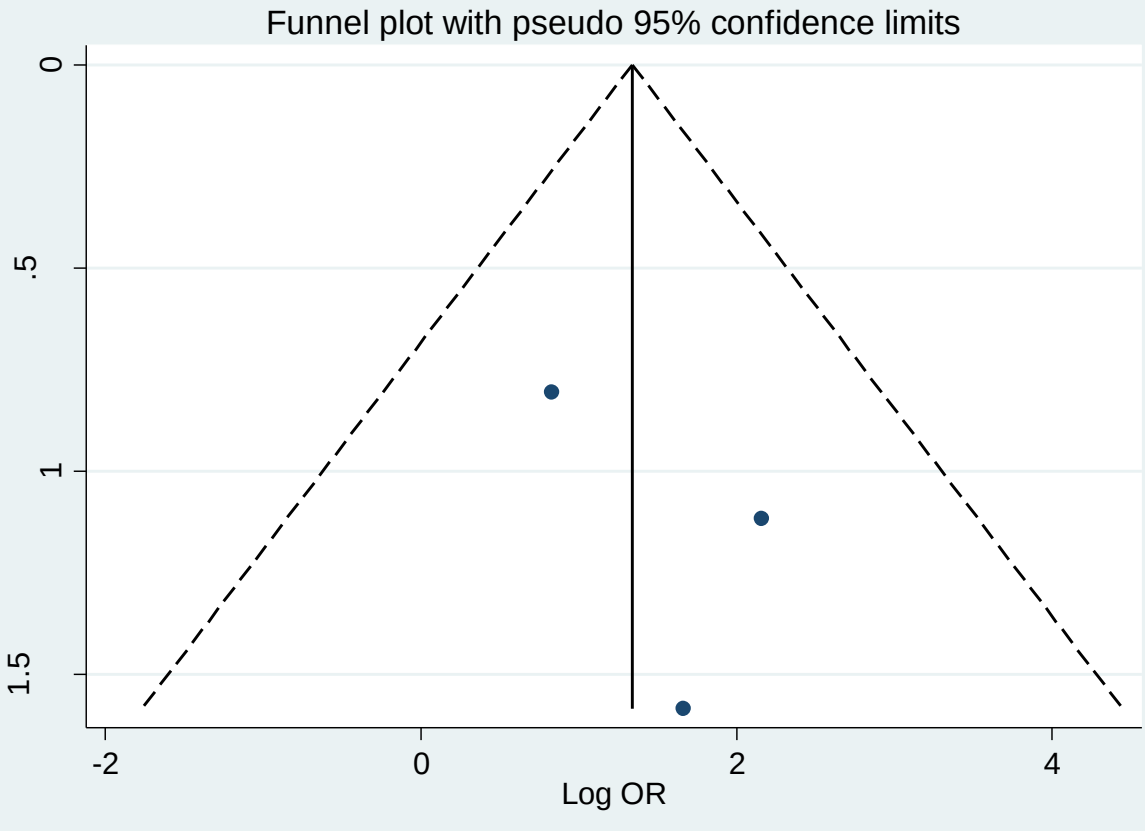


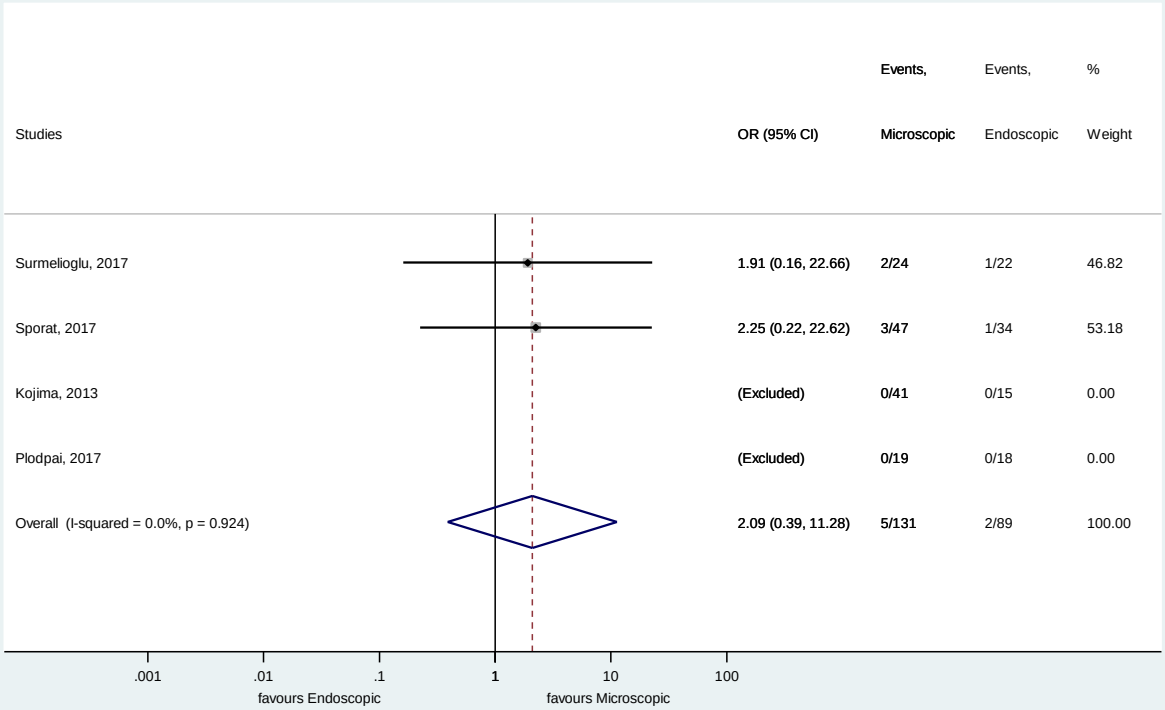


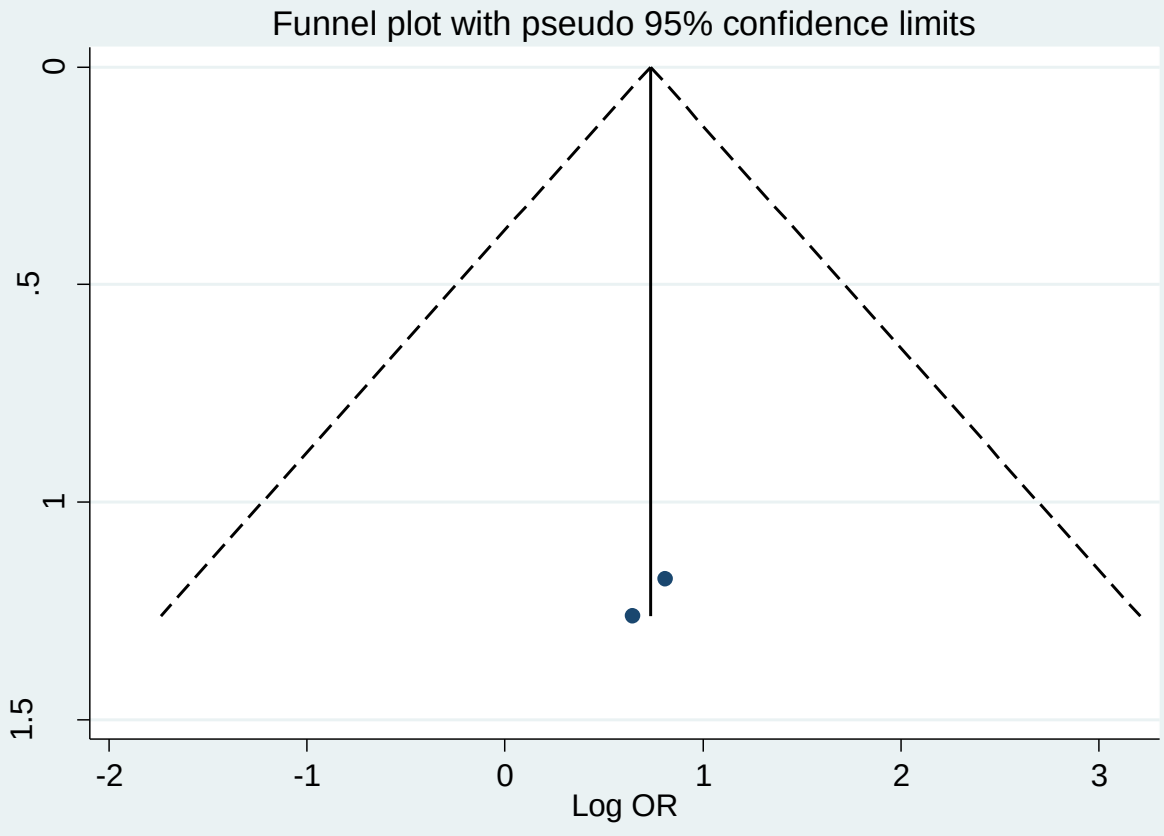
CHORDA TYMPANI INJURY



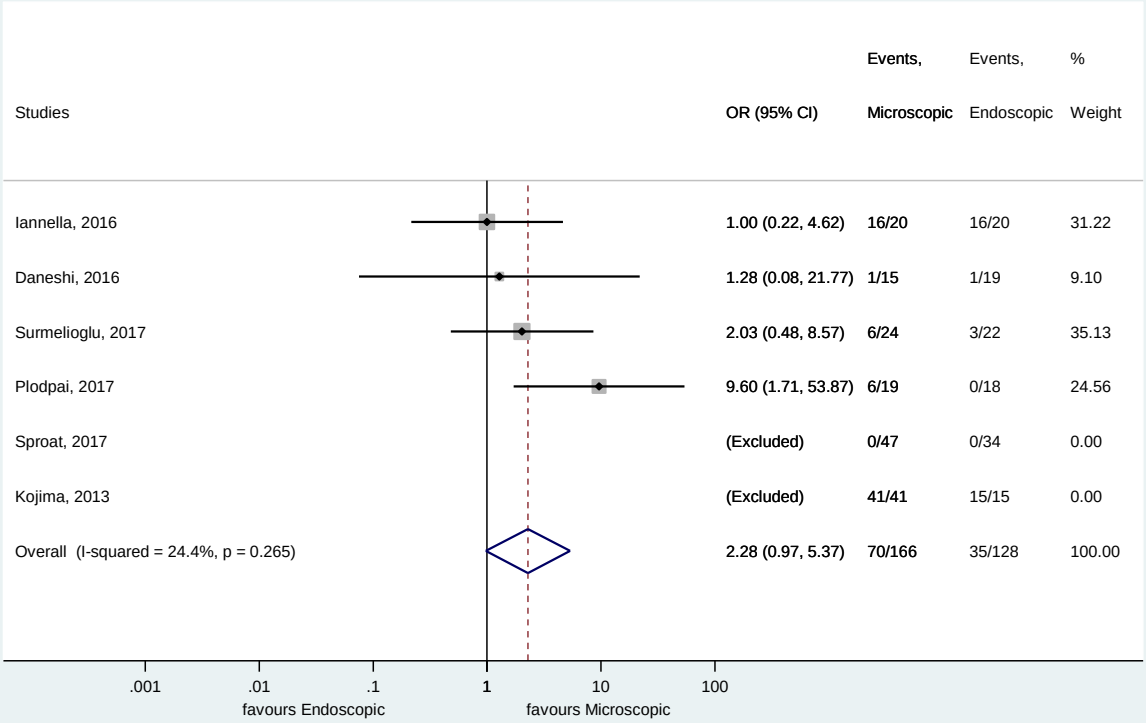


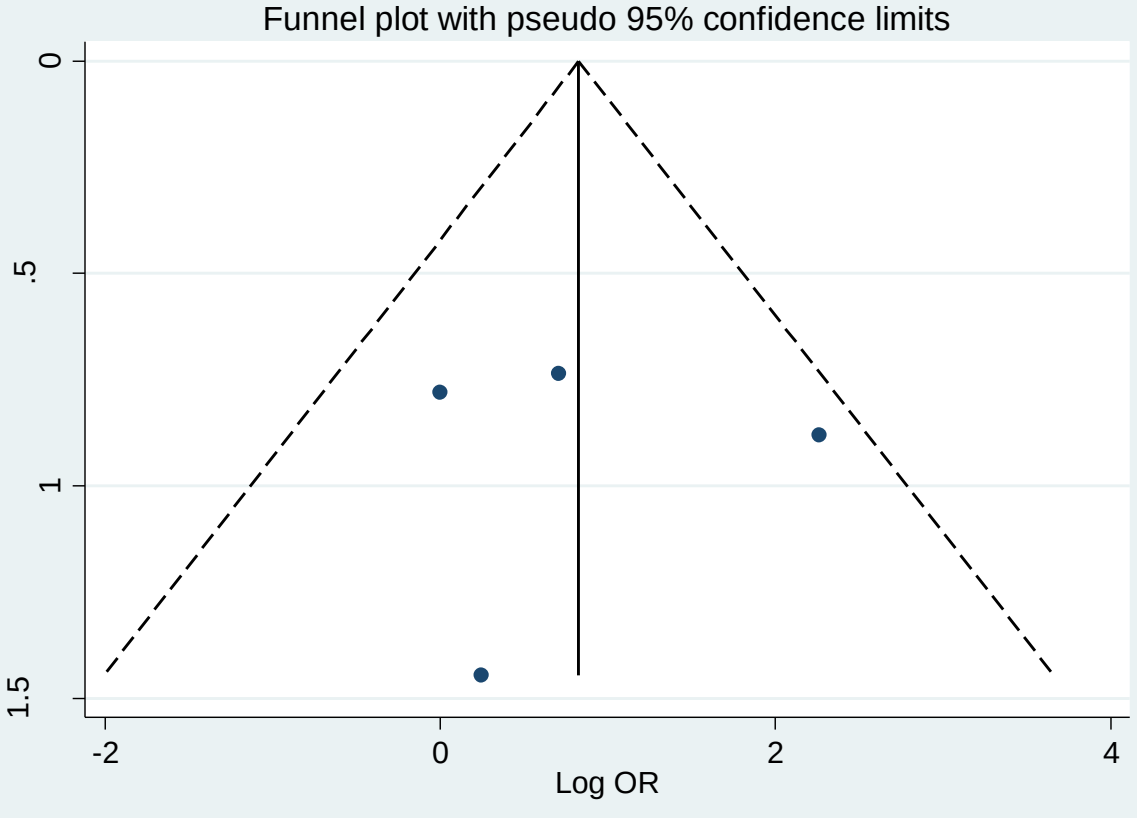
TYMPANIC MEMBRANE PERFORATION



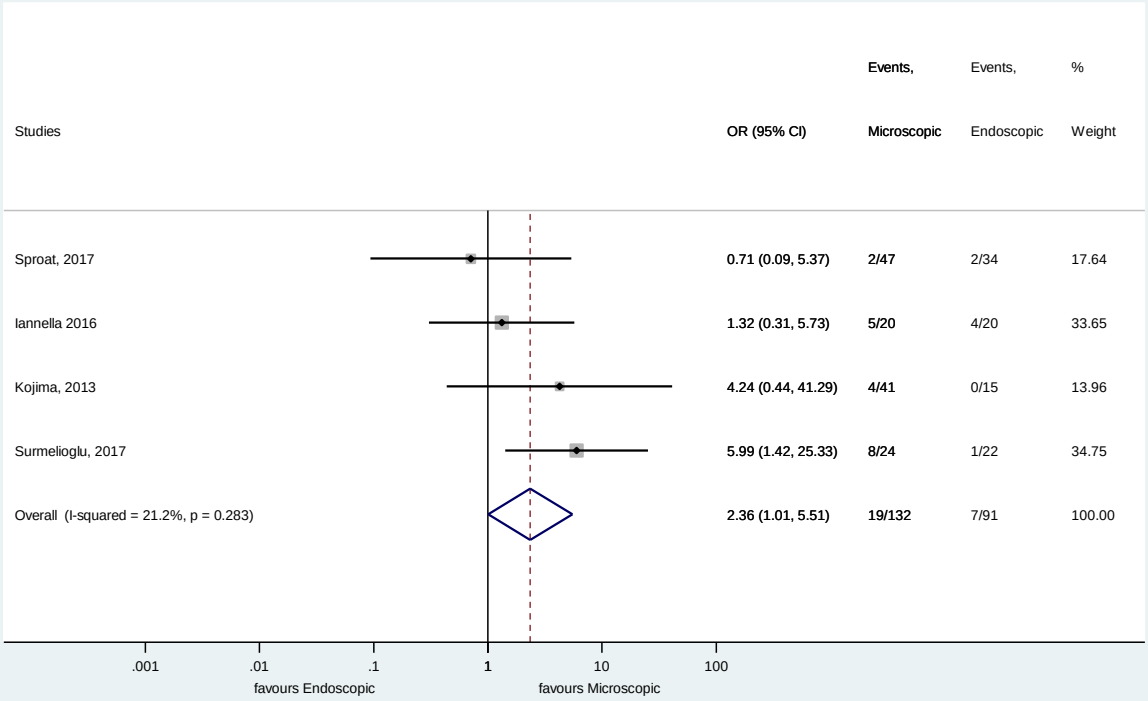


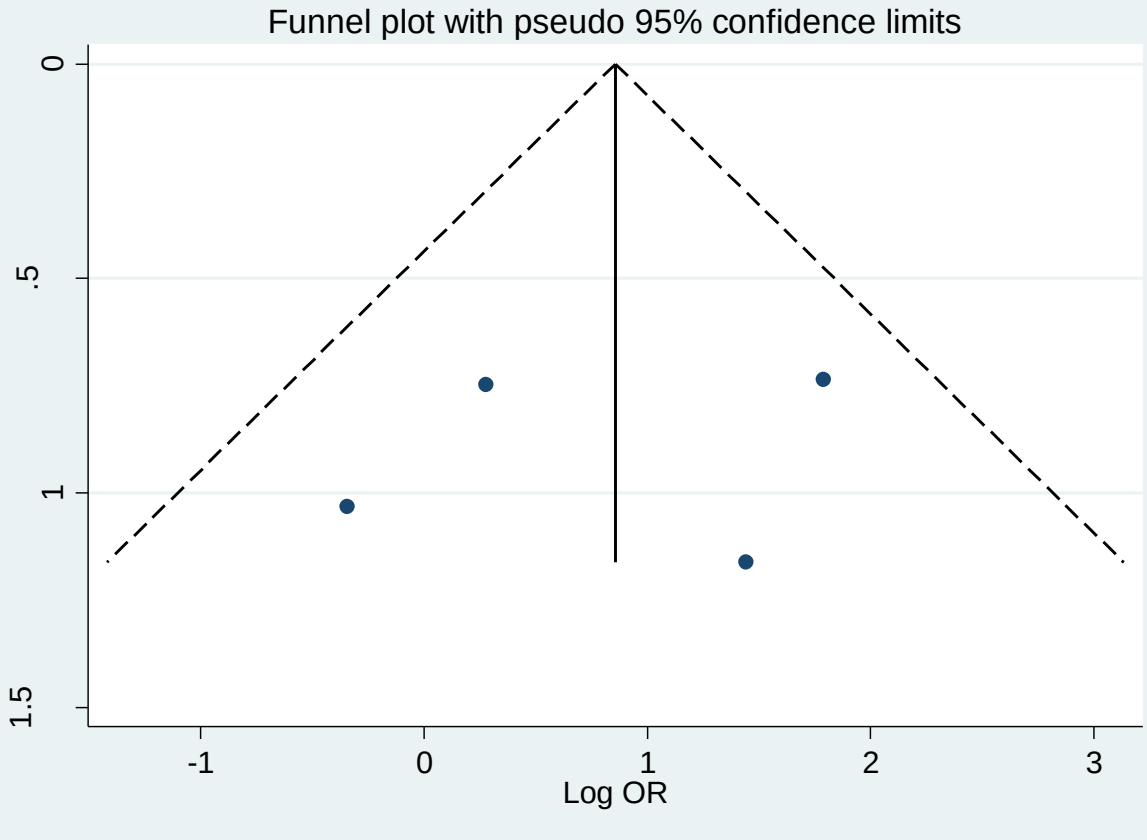
POST-OPERATIVE DIZZINESS





POST-OPERATIVE CHANGE IN TASTE





POST-OPERATIVE PAIN