EFFECTS IN LASER-ASSISTED STAPEDOTOMY

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Effects in laser-assisted stapedotomy

Effecten van stapedotomie uitgevoerd met een laser

(met een samenvatting in het Nederlands)

Proefschrift

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door

Digna Maria Anne Kamalski

geboren op 20 april 1981 te Geldrop

Promotores	Prof. Dr. W. Grolman
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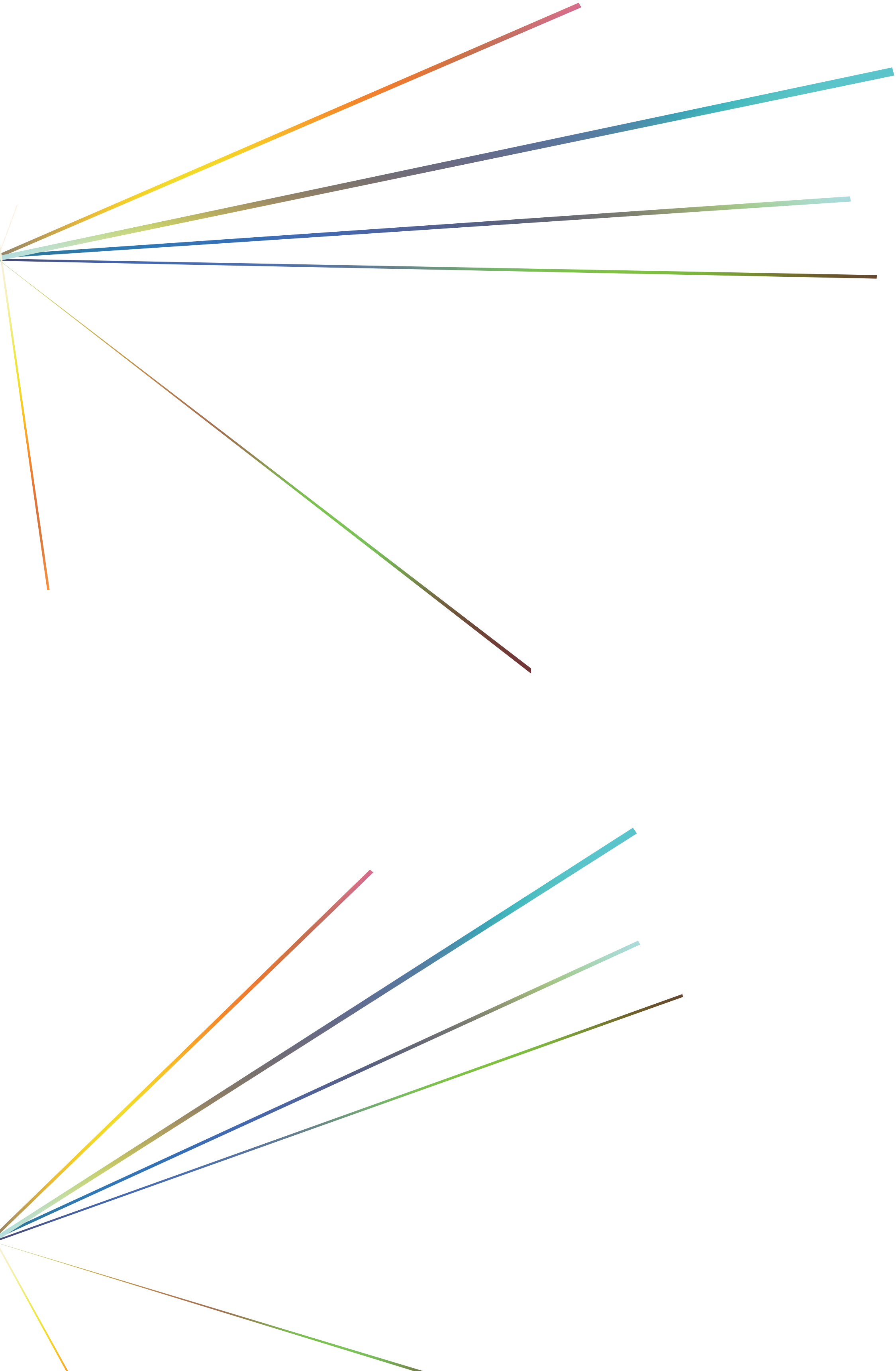

Contents

1

General Introduction

Otosclerosis

Otosclerosis or rather otospongiosis is a disorder of the bone homeostasis of the otic capsule. The disease is characterized by a process of *otospongiosis;* resorption of healthy bone and replacement with abnormal bone tissue. This process usually starts around the oval window, causing fixation of the stapes, resulting in conductive hearing loss (see **Figure 1**).[1-3] In believed to be the more advanced cases, the bone surrounding the cochlea can also be affected causing sensorineural hearing loss (SNHL).

Otosclerosis is considered a multifactor disease, caused by both genetic and environmental factors.[4,5] It causes 5-9% of all the cases with hearing loss and 18-22% of the cases with conductive hearing loss .[6] The disease is bilateral in 70-80% of the patients, it is progressive over time.[4,7] The onset of the hearing loss typically occurs between the ages of 15-45 years, with a higher prevalence in woman than men; (2:1).[8-11] Pregnancy seems to accelerate the process.[4,5] Clinical features are characterized by hearing loss, vertigo and tinnitus, or a combination of these symptoms.

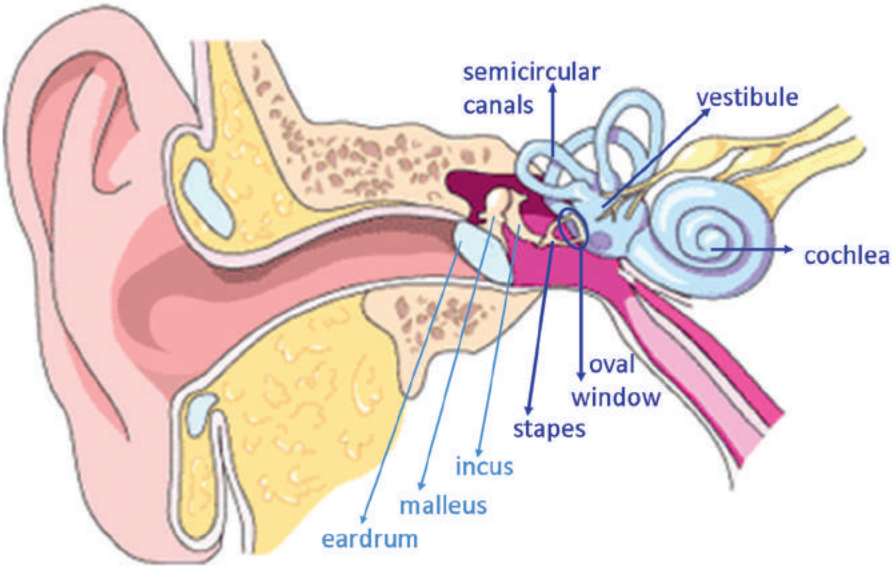

Figure 1 Anatomy of the ear

Stapedotomy

Treatment of conductive hearing loss caused by otosclerosis consists of either rehabilitation with hearing aids or performing surgery (stapedotomy). As most patients are relatively young and the average success rate for hearing restoration is high, they tend to choose surgery to improve hearing. Different surgical techniques can be applied.
In otosclerosis the ossicular chain is fixed due to fixation of the stapes footplate in the oval niche. During the surgical procedure to restore the conductive hearing the entire stapes can be removed from the oval niche, a technique called stapedectomy.[12] This procedure is not without risk, one of the more dangerous being leakage of fluids from the inner ear, possibly causing a deaf ear.[13]
A more refined technique seems to be the stapedotomy. In this technique a small hole, called fenestration, is made in the stapes footplate and the whole footplate is left in its oval niche. A prosthesis can be placed in this perforation, which is connected to the long process of the incus, regaining the mobility of the ossicular chain (see **Figure 2).** It needs to be noted that also this procedure is not without risk but they seem to be lower.[14]

Typically, these prostheses have a 0.4 to 0.6 mm diameter and a length on average of 4.5 mm although this sometimes varies (examples in **Figure 3**). The fenestration has to be made slightly wider than the diameter of the prosthesis. In conventional stapedotomy the fenestration is made by either micropick or a microburr. These techniques entail potentially substantial mechanical energy. Since the stapes is fragile, any mechanical force should be minimized to avoid serious trauma.

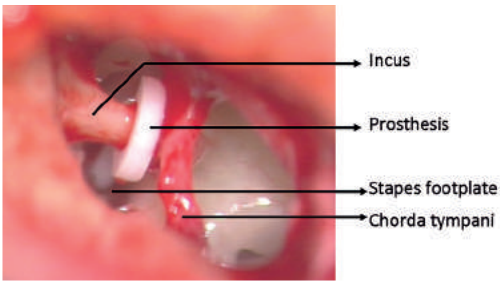

Figure 2 Prothesis connected to long process of incus, placed in a perforation in the stapes footplate

Figure 3 Examples of titanium (left) and Teflon (right) prostheses, used in stapedotomy

For example, an excessive mechanical force can break the stapes footplate, which might cause a floating footplate and, therefore, a risk of SNHL and vertigo. Further, the micro-burr generates substantial vibration and noise, possibly damaging the cochlear structures at its high frequency, again causing SNHL.
For this reason, a non-contact method for fenestration with the use of a laser seems to be preferable. Perkins was the first to describe in 1980, the use of a 480 nm Argon laser, to make multiple little perforations, of approximately 200 micron, in a round fashion.[15] Connecting these perforations, a fenestration of approximately 0.6 - 0.7 mm is created, large enough to fit the prosthesis. This is called the *rosette* technique, see **Figure 4**. This is a laser fiber delivered technique which allows for a very precise handling of the laser beam. Until recently some lasers types could not be fiber delivered and were therefore guided directly through the microscope using a manual manipulator. Frequently this setup was used with the one laser shot technique or *single shot* technique, by which with one laser shot a perforation of 0.7 mm is created. Critics of this last technique claim that de aiming accuracy is below of what is needed for stapes surgery resulting in a higher complication rate. Although there is no solid literature available on this topic, it is known that microscopes might have a tendency to show some undesired movement.

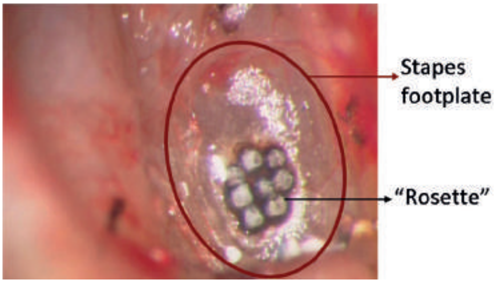

Figure 4 Intra-operative view of a stapes footplate in which a rosette of laser perforations is created (Courtesy of R Vincent [12])

Lasers

Background

Lasers have found their way into the medical field, especially in ophthalmology and dermatology. In the field of surgery (like Otorhinolaryngology, ORL), they have been proven to be the ideal source for delivering energy efficiently, through very small instruments, especially in the area of minimal invasive or keyhole surgery.

Many lasers are available nowadays, with different expected effects. However, all of them share three unique features:

1) Generation of monochromatic light, i.e. light of a specific wavelength. Thus, by selecting the specific wavelength, different effects can be achieved depending on the kind of tissue being treated. This allows for either high selectivity or homogenous distribution in large volumes. The emitted wavelength is dependent of the gain medium of the laser, which can be in all states; gas, liquid, solid or plasma.
2) Generation of a highly collimated output beam, i.e. parallel without diverging. This beam can be transported with miniature mirrors and applied to a spot without direct contact. Further, it enables efficient coupling into small optical fibers providing transportation e.g. through flexible endoscopes anywhere in the body.
3) Generation of high energy, capable of heating tissues to hundreds of degrees in very short amount of time, generating explosions and large mechanical stresses.[16,17]

In addition, the lasers can be characterized by the length of the laser output. In continuous wave lasers, light is emitted continuously as long as the system is switched on. Using a shutter the exit of the beam can be controlled from seconds down to milliseconds (10^{-3}), usually inducing a thermal effect heating the tissue.

In contrast to continuous wave laser, pulsed lasers emit a very short high intensity pulse on demand in the range from milliseconds down to femtoseconds (10^{-15}), usually inducing a mechanical explosive effect in combination with thermal effects depending on the number of pulses emitted shortly after each other.

Interaction of laser light with biological tissues

The way by which a laser interacts with a tissue being treated depends on the characteristics of both the laser and the tissue. The laser-tissue interaction results from a combination of four different processes illustrated in **Figure 5.**

- Absorption: Light energy is absorbed by the tissue contents (usually transferred to thermal energy, heating the tissue)
- Scattering: Light is spread through the tissue
- Transmission: Light leaves the tissue on the distal side (loss of laser energy)
- Reflection: Light changes its direction at the surface of the tissue (loss of laser energy)

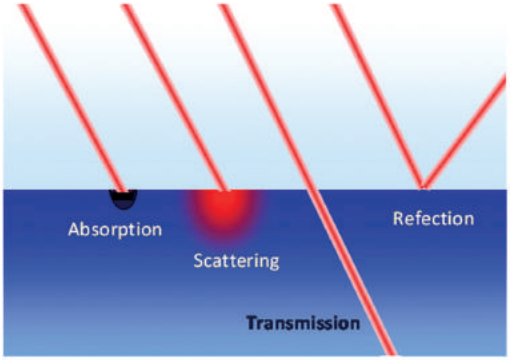

Figure 5 Laser-tissue interactions. Absorption, scattering, transmission and reflection

During the laser-tissue interaction, effects on the tissue being treated are a combination of desired and undesired effects. In stapedotomy the desired effect is absorption of the laser wavelength in the bone, causing ablation of the stapes footplate. Undesired effect during bone ablation can be sound generation when the fenestration is being made, since loud sounds can be damaging to high frequency hearing. Another undesired effect is damage to the vestibule, due to local absorption. Just beneath the stapes footplate part of the organ of equilibrium is located, the vestibule (see **Figure 1**). Damage to the vestibule, can cause vertigo. Further, the fluid of the vestibule, the perilymph, is in direct contact with the fluids in the cochlea. These effects in the vestibule might affect all inner ear functions, causing hearing loss and tinnitus as well.

It is possible to predict these possible undesired effects dependent to the laser wavelength. The energy not absorbed during bone ablation, will enter the perilymph of the vestibule. The level of absorption or transmission of the laser light in the perilymph will predict the possible side effects. **Figure 6** shows the absorption coefficient in water, as a function of the laser wavelength. The higher the water absorption coefficient is, the faster the laser light will be absorbed in the water. During absorption in water the energy usually turns into heat. Also mechanical effects can occur, such as bubble formation or generation of pressure waves. When the water absorption coefficient is low, the energy will barely be absorbed. The excess of energy is transmitted through the perilymph, until it reaches the neuro-epithelial cells in the border of the vestibule.
Figure 6 also shows the absorption of laser wavelength in haemoglobin. Typically, laser wavelengths with low water absorption coefficient are highly absorbed in pigmented, or haemoglobin-rich tissues. Since, neuro-epithelial cells are highly vascularized the absorption will occur at this level, causing local heating and damage to cell structures.

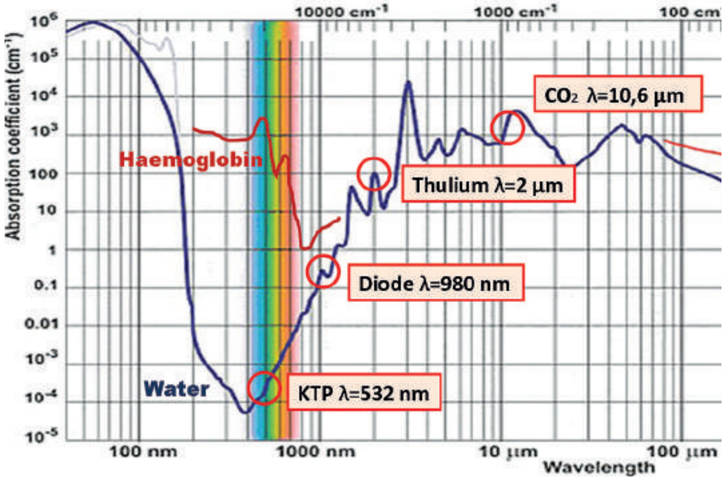

Figure 6 Absorption coefficient of laser light in water and haemoglobin, according to wavelength

Both mechanisms, transmission and absorption, can theoretically cause damage to inner ear structures, causing vertigo, tinnitus or hearing loss. It is not known, which of the laser wavelengths is potentially most harmful.

Laser settings

Knowing the laser and tissue characteristics the optimal settings for desired, with minimal undesired, effects can be predicted with this following relatively simple role of thumb: The amount of energy delivered in a particular volume of tissue in a particular amount of time. Which can be rephrased as: The amount of laser light (= energy) is being scattered and absorbed in tissue (spot size and depth = volume) within one or a short burst of laser pulses (= time).

The amount of laser energy delivered to an area of tissue is usually measured in Joules per square cm named fluence (J/cm^2) which relates to:

- o Pulse length: Longer pulses, increase fluency
- o Energy: More energy, increases fluency
- o Spot size: Larger spot size spreads the total energy, decreasing fluency

Typically the tissue effect goes through the phases illustrated in **Figure 7**. First the light is absorbed heating the tissue up to 100 °C (A). Tissue above 70 °C denatures or is coagulated (B), followed by tissue dehydration and vaporization around 100 °C. The moment at which most water is vaporized the temperature can rise instantly above 300 °C, causing decomposition and carbonization in the tissue.

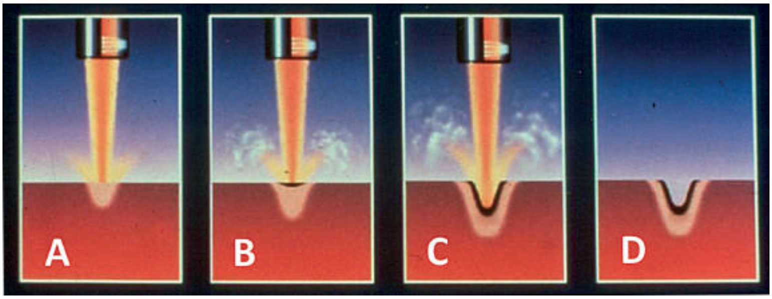

Figure 7 Laser tissue effects. Heating (A), coagulation (B), dehydration, vaporization and carbonization (C).

At this stage, since carbon absorbs all the laser light and vaporization is favored and a hole is created (C).
When a pulsed laser is used, the tissue is heated to 100 °C instantly and the water vaporizes explosively, bursting the cell membranes and creating a hole in the tissue without carbon formation. Depending on the laser settings and tissue the ablation process will pass through these phases.

Delivery system

The laser output beam is highly collimated, i.e. parallel without diverging. It can be used in free space, or guided through waveguides or collimated lenses. The choice of output delivery depends on the laser wavelength. When a laser is used in otology, the delivery method of the laser is extremely important. Since the length of the stapes footplate is only 3 mm, the laser delivery needs to be precise and the laser beam needs to pass the ear canal.
Classically used lasers in otology, such as KTP and Argon lasers, can be delivered through a silica fiber in a hand piece (see **Table 1**). It is an easy and precise method. Diode and Thulium lasers can also be delivered through a silica fiber.
On the other hand, a CO_2 laser has a 10.6 μm wavelength, which is highly absorbed in silica and, therefore, cannot be delivered with a silica fiber. To overcome this drawback, the CO_2 laser is classically delivered with an articulated arm, coupled to the microscope. The arm comprises mirrors to divert the laser light. With a joystick, a micromanipulator, the output beam can be aimed.[18] Since the CO_2 light is invisible, an aiming beam is added. This aiming beam will help the surgeon to locate the spot of application. This delivery method is not without risk. When adjusting the articulated arm too roughly, the aiming beam might get out of alignment with the laser beam. It can result in millimeters de-

flection, resulting in damage in surrounding structures, as the facial nerve. Hollow wave guides have recently become available for clinical use as an alternative to the articulated arms. They are similar to (solid core) silica fibers, although they comprise a thin hollow tube with a highly reflective inner coating for CO_2 light.[19]

Lasers in this thesis

In this thesis, four common lasers are compared; the 532 nm KTP, the 980 nm Diode, the 2 μm cw 'Thulium' and the 10.6 μm cw CO_2 laser. All these lasers are commonly used in different fields within ORL practice. The KTP laser is often used in otology and its effects are comparable to the 488 / 514 nm Argon laser.[17-19]

The Diode laser is a small practical laser, battery powered and relatively inexpensive. It is commonly used for vascular treatments (varicose veins) and hair removal.[20] In ORL practice it is used to treat difficult cases of epistaxis, as for instance patients with Rendu Osler Weber.[21,22]

The Thulium laser is used in oncology to excise squamous cell carcinomas in the head and neck region.[23] The CO_2 laser is often used in microsurgery, as it can be coupled to a surgical microscope and aimed with a micromanipulator. Especially in vocal cord lesions, benign or malignant, it has proved its use.[24,25] This laser is usually applied in pulsed mode. All the above mentioned lasers are used for stapedotomy. Due to their difference in wavelength, this thesis aims to compare these lasers. In **Table 1** the different characteristics of these lasers are shown. Clinical settings are the lowest settings needed to create a perforation. The total energy used differs between lasers depending on the bone ablating potential. The Thulium and Diode laser have lower bone ablating qualities and, therefore, higher fluencies.

Theoretically, the expected effects in the inner ear differ for each laser as described in the previous paragraphs. The CO_2 wavelength has the highest water absorption coefficient. Therefore, as soon as the excessive energy enters the vestibule, it is instantly absorbed. This can cause heating and mechanical effects and explosive bubble formation inducing pressure waves. The Thulium laser wavelength is also absorbed in the perilymph, but it is able to penetrate the perilymph more deeply.

The KTP laser wavelength is only barely absorbed until the carbonization phase is reached, it will mainly pass until it reaches the borders of the vestibule. These borders are aligned with neuro-epithelial cells. These sensory cells are highly vascularized. The high pigmentation of the haemoglobin causes absorption at this level. It might cause direct damage to these cells. The effects of the Diode laser are more difficult to predict, as both heating and direct damage might take place.

Table 1 Characteristics of the lasers in this thesis

	KTP	**Diode**	**Thulium**	**CO_2**
Wavelength	532 nm	980 nm	2 µm	10.6 µm
Delivery system	Silica fiber	Silica fiber	Silica fiber	- Articulated arm - Hollow wave guide
Clinical power settings	Rosette technique Pulses: 0.8 - 1.0 W; 100 ms	Rosette technique Pulses: 1.0 – 3.0 W; 100 ms	Rosette technique Pulses: 5.0 – 8.0 W; 100 ms	- Rosette technique 2.0 W; 100 ms - Single shot; 20.0 – 22.0 W; 50 ms
Experimental settings	1.0 W; 100 ms; spotsize 200 micron 318 J/cm^2	2.0 – 3.0 W; 100 ms spotsize 200 micron; 637-955 J/cm^2	6.0 W; 100 ms spotsize 365 micron 573 J/cm^2	2.0 W; 100 ms spotsize 250 micron 407 J/cm^2
Expected effects	Transmission through perilymph, direct damage to pigmented neuro-epithelial cells	Possibility of absorption, but also transmission through the perilymph	Deeper absorption in the perilymph, heating and mechanical effects	Direct absorption in the perilymph, heating and mechanical effects

Objective and Thesis outline

The main objective of this thesis is to identify the best laser to use in stapedotomy. In order to achieve this goal multiple aspects are to be taken into account. This leads to the following research questions:

1) In current literature;

- Does the use of a laser for fenestration during stapedotomy give better outcome compared to a conventional technique? **(Chapter 2)**
- Which laser used for fenestration during stapedotomy gives best outcome? **(Chapter 3)**

2) Which laser generates the least heating in the vestibule? **(Chapter 4, Chapter 6)**

3) Which laser shows the least mechanical and acoustic effects? **(Chapter 5, Chapter 6)**

4) Does irradiation with KTP laser cause direct damage to neuro-epithelial cells in the inner ear? **(Chapter 7)**

5) Which laser has the least effect on functionality of the inner ear function after laser-assisted cochleostomy? **(Chapter 8)**

6) How are the clinical results of the Thulium laser for stapedotomy compared to CO_2 laser? (**Chapter 9)**

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2

Laser versus Conventional Fenestration in Stapedotomy for Otosclerosis: A Systematic Review

I Wegner, DMA Kamalski, RA Tange, R Vincent, I Stegeman
GJM van der Heijden, W Grolman

Laryngoscope. 2014;124:1687-1693

Abstract

Objective: To assess hearing results and complications following primary stapedotomy in otosclerosis patients, comparing the use of laser and conventional techniques for fenestration.

Data Sources: PubMed, Embase, the Cochrane Library, CINAHL and Scopus.

Review Methods: A systematic bibliographic search was conducted. Studies reporting original data on the effect of laser fenestration, compared to conventional techniques, on closure of air-bone gap in patients undergoing stapedotomy were included. Directness of evidence and risk of bias of the selected articles was assessed. Studies with low directness of evidence, high risk of bias or both were not further analyzed. The absolute risks, risk differences and 95% confidence intervals were extracted only for studies with moderate to high directness of evidence and moderate to low risk of bias.

Conclusions: In total, 383 unique studies were retrieved. Eight of these (including 999 procedures) provided high or moderate directness of evidence and carried a moderate risk of bias and were considered eligible for data extraction. The included studies showed no consistent difference in postoperative air-bone gap closure or immediate postoperative vertigo. Both footplate fractures and sensorineural hearing loss appears to occur more frequently in the conventional group than in the laser group. Therefore we prefer laser above conventional methods for footplate fenestration in primary stapedotomy

Background

Otosclerosis is characterized by abnormal sponge-like bone growth in the middle ear, causing progressive hearing loss.[1] It mainly affects the ossicular chain and can be treated surgically by removing (part of) the stapes and replacing it with a prosthesis; stapedotomy and stapedectomy respectively. Although stapes surgery has proven to be a safe and effective treatment option for otosclerosis[2], permanent sensorineural hearing loss (SNHL) does occur in a small percentage of patients. The incidence of this dreaded complication following stapes surgery was less than 1% in large series.[3,4]

Over the years, stapedotomy fenestration techniques have evolved from the use of micro-instruments toward microdrill and more recently laser. Main advantages of the laser include the high precision of its application and the low risk of footplate mobilization as a result of the no-touch principle of this technique. Even though inner ear damage as a result of mechanical trauma is less likely, the potentially harmful effects of laser use should not be underestimated. Thermal effects on the perilymph associated with CO_2 laser use, acoustic trauma in Er-YAG laser use and penetration of the neuro-epithelium by the argon and KTP laser could all hypothetically result in inner ear dysfunction.[5-8]

The objective of this systematic review is to evaluate whether laser fenestration in primary stapedotomy for otosclerosis is safer than conventional fenestration techniques, measured by air-bone gap closure and adverse effects, including sensorineural hearing loss, vertigo, tinnitus and footplate fractures.

Methods

Retrieving studies – A systematic search in PubMed, Embase, the Cochrane Library, CINAHL and Scopus was conducted with assistance of a clinical librarian. Relevant synonyms for the search terms otosclerosis and laser were combined (see **Table 1**). Two assessors (IW and DK) independently excluded duplicate titles and screened title and abstract of the retrieved records for inclusion. Studies on the efficacy of laser stapedotomy, compared to conventional fenestration methods, in patients undergoing stapes surgery for otosclerosis were included. Conventional fenestration methods included the use of micro-instruments and microdrills, such as the Skeeter drill. Only reports of original study data were included; systematic reviews, opinion papers, animal or laboratory studies and case reports were excluded (see **Figure 1** for selection criteria).

Related publications were searched in PubMed, while Scopus and Web of Science were used for cross-reference checking for studies not identified by the initial literature search. Selected articles, related reviews, meta-analyses and guidelines were hand searched for relevant cross-references.

Table 1

Database	Search	Field
PubMed **The Cochrane Library** **CINAHL** **Scopus**	(otosclerosis OR otosclerotics OR otosclerotic OR otospongiosis OR otospongioses OR otospongiotic OR otospongeotic OR stapedotomies OR stapedotomy OR stapedectomies OR stapedectomy OR (stapes AND (surgery OR surgeries OR mobilization OR mobilisation)) OR (ossicular AND (replacement OR replacements))) AND (laser OR lasers OR KTP OR "potassium titanyl phosphate" OR CO_2 OR "carbon dioxide" OR "Er-YAG" OR erbium OR "yttrium aluminium garnet" OR diode OR argon OR thulium)	Title/ Abstract
Embase	(otosclerosis:ab,ti OR otosclerotics:ab,ti OR otosclerotic:ab,ti OR otospongiosis:ab,ti OR otospongioses:ab,ti OR otospongiotic:ab,ti OR otospongeotic:ab,ti OR stapedotomies:ab,ti OR stapedotomy:ab,ti OR stapedectomies:ab,ti OR stapedectomy:ab,ti OR (stapes:ab,ti AND (surgery:ab,ti OR surgeries:ab,ti OR mobilization:ab,ti OR mobilisation:ab,ti)) OR (ossicular:ab,ti AND (replacement:ab,ti OR replacements:ab,ti))) AND (laser:ab,ti OR lasers:ab,ti OR KTP:ab,ti OR "potassium titanyl phosphate":ab,ti OR CO_2:ab,ti OR "carbon dioxide":ab,ti OR "Er-YAG":ab,ti OR erbium:ab,ti OR "yttrium aluminium garnet":ab,ti OR diode:ab,ti OR argon:ab,ti OR thulium:ab,ti)	Title/ Abstract

Search for studies on the effect of laser fenestration, compared to conventional fenestration techniques, in primary stapedotomy for otosclerosis (date of search: May 22nd 2013)

Assessing studies – Using predefined criteria, two reviewers (IW and DK) independently assessed the selected studies for their directness of evidence and risk of bias (see **Table 2**). Directness of evidence concerned the applicability of the study findings for answering the clinical question and involved the evaluation of patients, compared treatments and outcomes: (1) patients, notably patients undergoing primary stapedotomy for otosclerosis, (2) treatment comparison, notably comparisons of any type of laser with

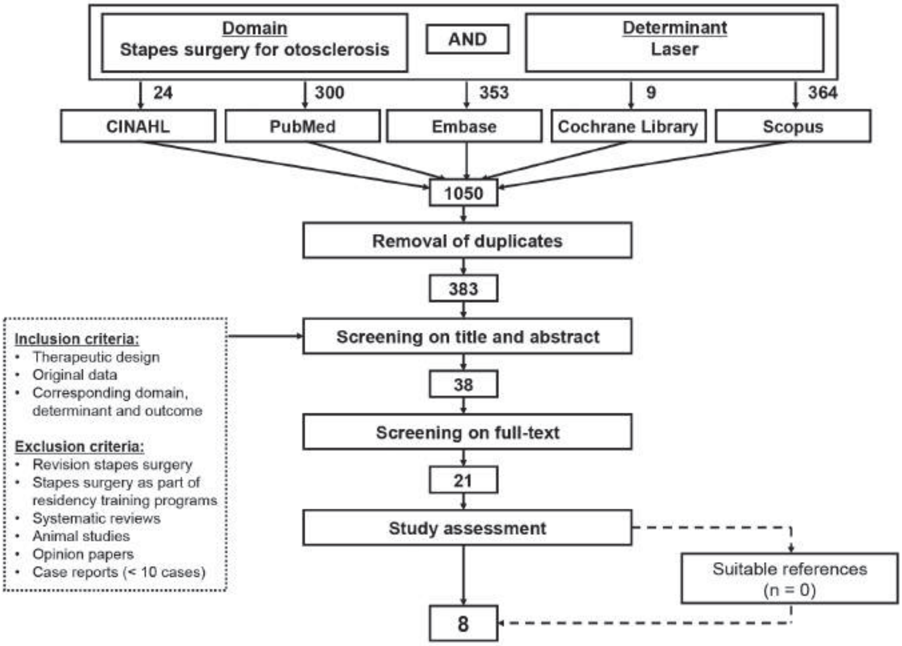

Figure 1 Flowchart for selection of studies on the effect of laser fenestration, compared to conventional fenestration, in primary stapedotomy for otosclerosis

conventional fenestration techniques, (3) outcomes, notably our outcome of interest was air-bone gap closure. Studies were classified as having high, moderate or low directness of evidence if they complied with all three, two or one of these criteria respectively. With the risk of bias assessment the extent of selection and information bias was established. Assessment of risk of bias involved evaluation of selection bias, notably (1) concealed treatment assignment with random allocation and (2) completeness of reported data; and information bias, notably (3) blinding of treatment nature and outcome assessment, (4) standardization of treatment and (5) standardization of outcome assessment. Studies were classified as having a low risk of bias if they satisfied all of these criteria, moderate risk of bias if they satisfied at least criteria 1 or 2 plus one of the criteria for information bias, and the remainder was classified as high risk of bias. When an item of the study assessment was not reported, it was rated 'unclear'. When an item was reported, it was classified as either 'satisfactory' or 'unsatisfactory'. Initial discrepancies between independent reviewers were resolved by discussion and reported results are based on full consensus. Studies with either or both low directness of evidence and high risk of bias were excluded for further review.

Table 2

Study	Sample size of study (n)	Study design	**Directness of evidence**				**Risk of bias**					
			Patients	Treatment	Outcome	Directness of evidence	Treatment allocation	Blinding	Standardization (T)	Standardization (O)	Complete data	Risk of bias
Häusler (1996)[6]	83	RCS	●	●	●	H	?	?	●	●	●	M
Badran (2006)[15]	85	RCS	●	●	●	H	?	?	●	○	●	M
Barbara (2011)[16]	82	RCT	●	●	●	H	?	?	?	●	●	M
Moscillo (2006)[23]	110	RCS	●	●	●	H	?	?	?	●	●	M
Matkovic (2003)[22]	80	PCS	●	●	●	H	?	?	?	●	●	M
Motta (2002)[24]	451	RCS	●	●	●	H	?	?	○	●	●	M
Just (2012)[20]	48	PCS	●	●	○	M	○	○	?	●	●	M
Cuda (2009)[18]	60	PCS	●	●	○	M	○	○	●	●	●	M
Singh (2012)[31]	20	RCS	●	●	●	H	?	?	●	●	?	H
Malafronte (2011)[21]	83	PCS	●	●	●	H	○	?	?	?	●	H
Nguyen (2008)[25]	253	RCS	●	●	●	H	?	?	●	●	○	H
Galli (2005)[19]	70	PCS	●	●	●	H	?	?	●	?	?	H
Parrilla (2008)[26]	152	RCS	?	●	●	M	?	?	●	●	?	H
Rauch (1992)[27]	100	RCS	●	●	●	H	?	?	?	○	○	H
Brase (2013)[17]	302	RCS	●	●	○	M	?	?	?	●	○	H
Szymanski (2007)[33]	420	RCS	●	●	○	M	?	?	●	?	?	H
Arnoldner (2006)[14]	151	RCS	○	●	●	M	?	?	?	●	○	H
Shabana (1999)[29]	350	RCS	?	●	●	M	○	?	?	○	?	H
Silverstein (1989)[30]	47	RCS	●	○	●	M	?	?	○	○	○	H
Ryan (2009)[28]	19	RCS	●	?	○	L	?	?	?	?	?	H
Somers (2006)[32]	336	PCS	?	●	○	L	?	?	?	●	?	H

Study assessment of studies on the effect of laser fenestration, compared to conventional fenestration, in primary stapedotomy for otosclerosis

Study assessment of studies on the effect of laser fenestration, compared to conventional fenestration, in primary stapedotomy for otosclerosis

- *Study Design*
RCT = randomized controlled trial; PCS = prospective cohort study; RCS = retrospective cohort study; CS = cohort study, unclear whether in prospect or retrospect; H = high; M = moderate; L = low.

- *Directness of evidence*
Patients: ● = primary stapedotomy for otosclerosis; ○ = primary stapedectomy, revision surgery for otosclerosis,stapes surgery as part of residency training programs, other.Treatment: ● = any type of laser compared with conventional technique; ○ = other. Outcome: ● = recovery of conductive hearing loss measured by closure of air-bone gap; ○ = other.

- *Risk of bias*
Randomization: ● = adequate randomization (e.g. random number table or coin toss); ○ = no adequate randomization (e.g. sequence generated by date of admission or allocation by judgment of clinician); ? = unclear, no information provided.Treatment allocation: ● = adequate concealment (e.g sealed envelopes); ○ = no adequate concealment; ? = unclear, noinformation provided. Blinding of fenestration method uring postoperative pure-tone audiometry and interpretation of audiometry: ● = patients and clinicians blinded; ○ = only patients blinded or no blinding; ? = unclear, no information provided. Standardization (T) of surgical procedure and laser settings: ● = yes; ○ = no; ? = unclear, no information provided. Standardization(O) of postoperative pure-tone audiometry with regard to frequencies used and follow-up duration: ● = yes; ○ = no; ? = unclear, no information provided.Completeness of outcome data for primary outcome: ● = below 10% missing data; ○ = 10% or more missing data; ? = unclear, no information provided

Data extraction – For the included studies, two authors (IW and DK) independently extracted descriptive data of patients and interventions. For the outcomes of interest the absolute risks and their risk differences with the corresponding 95% confidence intervals (95%CIs) were extracted. The primary outcome measure was closure of the air-bone gap to within 10 decibels or less, preferably for the frequencies 500, 1000, 2000 and 3000 or 4000 Hz, which is generally considered a successful outcome of stapes surgery in literature in the sense of the surgeon's surgical performance.[4,9-11] According to the Committee on Hearing and Equilibrium, follow-up should be at least one year for this outcome measure since results change over time and long-term results provide a more realistic prognosis.[12] Secondary outcome measures were sensorineural hearing loss, vertigo, tinnitus and fractured footplate. Preferably absolute risks were extracted. If these were not given or could not be recalculated, the findings as reported in the article were presented.

Results

Retrieving studies – A total of 1050 titles was retrieved, of which 383 were unique studies (see **Figure 1**; date of last search was May 22nd 2013). Papers published in Chinese were excluded.[13] After selection based on title and abstract, and subsequent full-text screening, 21 articles.[6,14-33] were initially considered eligible for answering our question. Cross-reference checking revealed no additional articles.

Assessing studie – The directness of evidence was found low or moderate for ten studies and high for eleven studies (see **Table 2**). Assessing all 21 studies, it was unclear whether all patients had undergone primary stapes surgery in three studies[26,29,32], more than one type of laser was used without performing subgroup analyses in one study[30] and air-bone gap closure was not reported in six studies.[17,18,20,28,32,33] In eight studies[6,15,16,18,20,22-24] the risk of bias was moderate, while it was high in the other thirteen. Adequate randomization, treatment allocation and blinding were either not achieved or no information was provided regarding these criteria in any of the 21 included studies. Standardization of treatment was achieved in eight of the included studies[6,15,18,19,25,26,31,33] and standardization of postoperative pure-tone audiometry in thirteen studies.[6,14,16-18,20,22-26,31,32] In the studies that did not meet these criteria, laser settings were not adequately described or standardization of follow-up duration lacked. For five studies[14,17,25,27,30] a large amount of outcome data was missing and in another seven studies[19,26,28,29,31-33] it was unclear whether outcome data was complete. Selective reporting cannot be ruled out in the

retrospective cohort studies. Two retrospective studies explicitly reported that patients lacking adequate audiological follow-up were excluded.[15,27] Thirteen studies with either or both low directness of evidence and high risk of bias were excluded for further review.[14,17,19,21,25-33]
Eight studies that carried moderate risk of bias were included for further review, of which six provided evidence of high directness[6,15,16,22-24] and the other two of moderate directness.[18,20] Air-bone gap closure was not reported in the studies with moderate directness.[18,20] Conclusions were based on these eight studies. The study reported by Häusler et al.[6] failed the least risk of bias criteria. Therefore, we put most trust in the data presented in this study.

Data extraction – The eight selected studies included in total 999 procedures. There are major dissimilarities between studies regarding type of laser, type of conventional fenestration technique and follow-up duration. In most studies the CO_2 laser was used.[15,18,20,22-24] However, different laser settings were used in these studies (see **Table 3** for reported laser settings). A difference in laser settings most likely influences outcome, for example as a result of more heat generation on and through the footplate.[34] Argon[6] and Thulium[16] were used in the remaining two studies.
The extracted outcome data of the included studies are described in **Table 4**. Risk differences are positive when results favor laser fenestration and negative when results favor conventional fenestration. In the study performed by Häusler et al.[6], the difference in postoperative air-bone gap closure is in favor of laser fenestration, with a risk difference of 12 [95%CI 9.5 , 14.5]. Another five studies report risk differences for postoperative air-bone gap closure between -13 [-10.1 , -15.9] and 13.7 [12.5 , 14.9][15,16,22-24], some of which are in favor of laser fenestration[16,22-24] and some of which are in favor of conventional fenestration.[15]
Sensorineural hearing loss occurred less frequently in the laser group in the study performed by Häusler et al. with a risk difference of 1.5 [1.3 , 1.7]. Another three studies report risk differences for sensorineural hearing loss between 1.2% [1.2 , 1.2] and 2.8% [2.4 , 3.2].[15,23,24]
Häusler et al. report a risk difference for postoperative vertigo of 1.5 [1.3 , 1.7]. Another three studies evaluating immediate postoperative vertigo report risk differences between -3.3 [-2.5 , -4.1] and 29 [22.8 , 35.2].[15,18,22]. In one of these three studies, postoperative vertigo occurred less frequently in the conventional group[18], whereas in the other two risk differences were in favor of laser fenestration.[15,22]
Immediate postoperative tinnitus was evaluated in two studies[15,22] and seems to occur more frequently in patients treated with the use of the laser.

Table 3 Study descriptives of studies on the effect of laser fenestration, compared to conventional fenestration, in primary stapedotomy for otosclerosis

Study	Study design	Laser (n)	Control (n)	Laser type	Laser settings	Control group method	Frequencies pure-tone audiometry	Follow-up duration
Häusler (1996)[6]	RCS	54	29	Argon	1.5 W, 0.1 s, 0.6 mm 53 J/cm^2	Skeeter drill with 0.6 mm microbur	0.5, 1 and 2 kHz	8 weeks
Badran (2006)[15]	RCS	36	49	CO_2	20 W, 0.05 s, 0.7 or 0.8 mm, continuous 260 J/cm^2	Mechanical perforator or Skeeter drill with 0.8 mm microbur	0.5, 1, 2 and 4 kHz	Last postoperative PTA within 1 year
Barbara (2011)[16]	RCT	10	29	Thulium	550 mu	Skeeter drill with 0.6 mm microbur	0.25 to 2 kHz	1 month
Moscillo (2006)[23]	RCS	65	45	CO_2	NA	Microdriller	0.5, 1, 2 and 3 kHz	1 month and every 6 months
Matkovic (2003)[22]	PCS	40	40	CO_2	20 W, 0.03 s	NA	0.5, 1, 2 and 3 kHz	6 months
Motta (2002)[24]	RCS	282	169	CO_2	10-12 W, 0.05 s, 0.7 mm, single defocused impulse (Zeiss) 130-156 J/m^2 5 W, 0.05 s, 0.7 mm, superpulse (Sharplan) or 18 W, 0.6 mm, continuous (Flashscan)	Richards mod. Shea microdrill with 0.7 mm microbur	0.5, 1, 2 and 3 kHz	At least 1 year
Just (2012)[20]	PCS	35	13	CO_2	20 W, 40 ms, 0.6 mm, continuous mode.	Manual perforator	0.5, 1, 2 and 3 kHz	14-21 days and 6 weeks
Cuda (2009)[18]	PCS	30	30	CO_2	20 W, 0.05 s, 0.7 mm, single shot	Skeeter drill with 0.7 mm microbur	0.5, 1, 2 and 4 kHz	1 month

n = number of procedures, NA = not available, PTA = pure-tone audiometry

Table 4 Results of studies on the effect of laser fenestration, compared to conventional fenestration, in primary stapedotomy for otosclerosis

Study	Laser (n)	Control (n)	Follow-up	ABG closure (< 10dB)			Adverse events			
				Laser (%)	Control (%)	Risk difference (% [95%CI])	Outcome	Laser (%)	Control (%)	Risk difference (% [95%CI])
Häusler (1996)[6]	Argon (54)	Skeeter (29)	8 weeks	98	86	12 [9.5 , 14.5]	Vertigo	1.9	3.4	1.5 [1.3 , 1.7]
							SNHL	1.9	3.4	1.5 [1.3 , 1.7]
Badran (2006)[15]	CO_2 (36)	Skeeter or microperforator (49)	< 1 year	53	66	-13 [-10.1 , -15.9]	Vertigo	2.8	12.2	9.4 [7.5 , 11.3]
							Tinnitus	2.8	2	-0.8 [-0.5 , -1.1]
							Footplate fracture	0	8.2	8.2 [6.6 , 9.8]
							SNHL	0	2	2 [1.7 , 2.3]
Barbara (2011)[16]	Thulium (10)	Skeeter (29)	1 month	90	86.2	3.8 [3.1 , 4.5]	-	-	-	-
Moscillo (2006)[23]	CO_2 (65)	Microdrill (45)	3 years	90.6	86.2	4.4 [3.7 , 5.1]	SNHL	1.6	4.4	2.8 [2.4 , 3.2]
Matkovic (2003)[22]	CO_2 (40)	NA (40)	6 months	82.6	75.3	7.3 [5.8 , 8.8]	Vertigo	26	55	29 [22.8 , 35.2]
							Tinnitus	7.5	0	-7.5 [-5.7 , -9.2]
							Footplate fracture	0	12.5	12.5 [9.9 , 15.1]
Motta (2002)[24]	CO_2 (282)	Shea microdrill (169)	> 1 year	87.4	73.7	13.7 [12.5 , 14.9]	Vertigo	0	9.5	9.5 [8.7 , 10.3]
							SNHL	1.8	3	1.2 [1.2 , 1.2]
Just (2012)[20]	CO_2 (35)	Microperforator (13)	14-21 days and 6 weeks	-	-	-	-	-	-	-
Cuda (2009)[18]	CO_2 (30)	Skeeter drill (30)	1 month	-	-	-	Vertigo	10	6.7	-3.3 [-2.5 , -4.1]
							Footplate fracture	0	0	0

When risk difference is positive, this favors laser. n = number of procedures; ABG = air-bone gap; SNHL = sensorineural hearing loss

Risk differences for postoperative tinnitus in these two studies were -0.8% [0.5 , 1.1] and -7.5% (5.7 , 9.2].
A decreased incidence of footplate fracture was witnessed in the laser group in two studies, with risk differences of 8.2% [6.6 , 9.8] and 12.5% [9.9 , 15.1].[15,22]

Discussion

The amount of available studies on the effect of laser fenestration, compared to conventional fenestration techniques, on postoperative air-bone gap closure is substantial. The eight included studies all carry a moderate risk of bias, while the directness of evidence is high for six of the included studies. Some of the included studies show a difference in postoperative air-bone gap closure and immediate postoperative vertigo that favors the conventional approach. However, footplate fractures and sensorineural hearing loss also occur more frequently in the conventional group than in the laser group, while tinnitus appears to occur more frequently in the laser group. Taken into consideration the potential risks of the conventional methods, we would prefer to use the laser for fenestration instead of conventional techniques.

In interpreting the findings, the following considerations need to be taken into account. *First*, the designs of the included studies differ in their approach to the type and settings of the laser, the conventional fenestration technique, the choice of pure-tone audiometric frequencies and follow-up duration. In most studies the duration of follow-up was short and never reached one year. Furthermore, different piston types and sizes were used. Several studies showed that choice of piston diameter and type of prosthesis affect hearing outcome.[35,36] *Second*, all of the included studies carry moderate to high risk of bias due to lack of randomization, treatment allocation, blinding of observations and poorly standardized treatment and test procedures. Furthermore, selective reporting, as a result of excluding cases lacking adequate follow-up, cannot be ruled out in the retrospective cohort studies. High risk of bias can lead to overestimation or underestimation of true intervention effects. Therefore, the results from studies with high or moderate risk of bias cannot be trusted. *Third*, the sample sizes, varying from 48 to 451 ears, are rather small and in the majority of studies sample sizes were uneven. Given that sensorineural hearing loss occurs in less than 1% of stapedotomies, very large series are needed to make reliable statements about this outcome measure. Small sample sizes can lead to overestimation or underestimation of intervention effects as well. *Last*, adverse events were not systematically evaluated in all of the included studies. It seems likely that postoperative vertigo and tinnitus occur less often in laser-assisted stapedotomy as a result of the non-contact principle. In particular because footplate fracture and sensorineural hearing loss do occur less frequently following laser-assisted stapedotomy.

Conclusion and recommendation

To date, there is no evidence that either laser fenestration or conventional fenestration techniques is superior to the other technique with regard to hearing outcome or immediate postoperative vertigo. Therefore, becoming comfortable with one technique and use what works best for them seems most appropriate for surgeons. There does, however, seem to be an increased risk of footplate fracture and sensorineural hearing loss following the use of micro-instruments or microdrill. Taken into account this risk of harm, the authors prefer laser over conventional methods for footplate fenestration in primary stapedotomy. However, future randomized trials and prospective follow-up of well-defined cohorts are needed to provide low risk of bias and high directness of evidence for firm practice statements.

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chapter

2

3

Outcomes of Different Laser Types in Laser-assisted Stapedotomy: A Systematic Review

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Abstract

Objective: To assess hearing results and complications following primary stapedotomy in otosclerosis patients, comparing different laser types.

Data Sources: Pubmed, Embase, the Cochrane Library, CINAHL and Scopus

Study Selection: A systematic bibliographic search was conducted to identify all original articles, comparing hearing outcome between different lasers used for fenestration in stapedotomy.

Data Extraction: Directness of evidence and risk of bias of the selected articles were assessed. Studies with low or moderate directness of evidence, or high risk of bias, were not further analyzed.

Data Synthesis: The absolute risks, risk differences and 95% confidence intervals were extracted only for the studies with high directness of evidence and moderate to low risk of bias.

Conclusions: A total of 383 unique articles were retrieved. Four studies provided direct evidence, whereas all studies carried moderate to high risk of bias. After exclusion of the studies that did not provide direct evidence and/or carried high risk of bias, two studies were considered eligible for data extraction. This best available evidence shows a slightly better Air-Bone Gap closure for CO_2 laser compared to KTP laser, but the clinical relevance is unclear. The risk difference of 28.1% [95% CI, 22.8, 33.4] between CO_2 and Er-YAG, favors CO_2 laser. Unfortunately, this current best available evidence is insufficient to draw any definitive conclusions on which laser to use for fenestration in stapedotomy.

Introduction

Perkins[1] introduced the Argon laser stapedotomy in 1980, using laser to perforate the footplate. In comparison to conventional techniques, the use of lasers minimizes risk of mechanical trauma to the middle and inner ear. Multiple types of lasers have been suggested, in both visible and invisible spectra, each with different characteristics.

The Argon (488, 514 nm) and potassium titanyl phosphate KTP;532 nm): laser have similar wavelengths in the visible spectrum. They are not well absorbed in water, but are highly absorbed in pigmented areas, such as the neuro-epithelium in the vestibule. Potential damage could occur at this level, causing vertigo. Non visible wavelengths, such as Er-YAG (2900 nm) and CO_2 (10600 nm) have different characteristics, with other potential adverse effects. Due to its wavelength, Er-YAG is highly absorbed in bone, causing explosive ablation of bone, generating a shockwave through the inner ear. CO_2 laser light is effectively absorbed in water, diminishing penetration, but generating heat, which can potentially harm inner ear function. Animal and laboratory tests have confirmed these absorption patterns.[2-5] The clinical relevance of these findings remains uncertain.

Many authors have published their individual results in laser-assisted stapedotomy, mainly focusing on hearing results. However, it remains unclear which laser is best suited for the purpose of fenestrating the footplate. The goal of this study is to identify the laser which gives best hearing results, measured by air-bone gap (ABG) closure. Secondary outcome measures include adverse effects, such as sensorineural hearing loss, tinnitus and vertigo.

Methods

Retrieving studies – A systematic search in PubMed, Embase, the Cochrane Library, CINAHL and Scopus was conducted with assistance of a clinical librarian. Relevant synonyms for the search terms stapedotomy and laser were combined (see **Table 1**). Two assessors (IW and DK) independently excluded duplicate titles and screened title and abstract of the retrieved records for inclusion. Studies on the efficacy of laser stapedotomy, comparing two different laser types, in patients undergoing primary stapedotomy for otosclerosis were included. Only reports of original study data were included; systematic reviews, opinion papers, animal or laboratory studies and case reports were excluded (see **Figure 1** for selection criteria). Related publications were searched in PubMed, while Scopus and

Web of Science were used for cross-reference checking for studies not identified by the initial literature search. Selected articles, related reviews, meta-analyses and guidelines were hand searched for relevant cross-references.

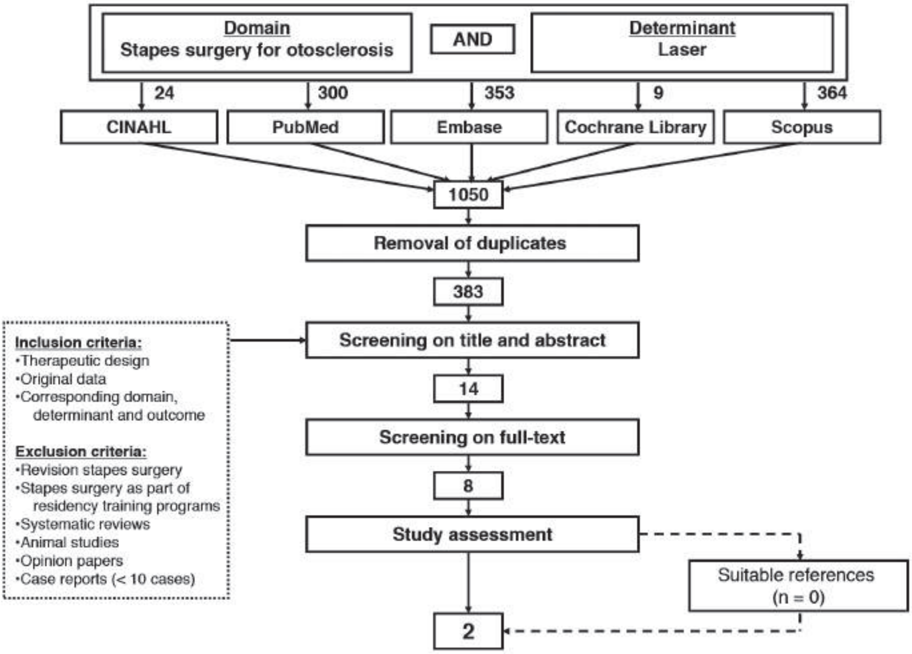

Figure 1 Flowchart for selection of studies on the effect of laser fenestration, compared to conventional fenestration, in primary stapedotomy for otosclerosis

Assessing studies – Using predefined criteria, two reviewers (IW and DK) independently assessed the selected studies for their directness of evidence and risk of bias (see **Table 2**). Directness of evidence concerned the applicability of the study findings for answering the clinical question and involved the evaluation of patients, compared treatments and outcomes: (1) patients, notably patients undergoing primary stapedotomy for otosclerosis, (2) treatment comparison, notably comparisons of two different types of laser, (3) outcomes, notably our outcome of interest was air-bone gap closure after at least 3 months of follow-up. Studies were classified as having high, moderate or low directness of evidence if they complied with all three, two or one of these criteria respectively. With the risk of bias assessment the extent of selection and information bias was established.

Table 1

Database	Search	Field
PubMed **The Cochrane Library** **CINAHL** **Scopus**	(otosclerosis OR otosclerotics OR otosclerotic OR otospongiosis OR otospongioses OR otospongiotic OR otospongeotic OR stapedotomies OR stapedotomy OR stapedectomies OR stapedectomy OR (stapes AND (surgery OR surgeries OR mobilization OR mobilisation)) OR (ossicular AND (replacement OR replacements))) AND (laser OR lasers OR KTP OR ”potassium titanyl phosphate” OR CO2 OR “carbon dioxide” OR “Er-YAG” OR erbium OR “yttrium aluminium garnet” OR diode OR argon OR thulium)	Title/ Abstract
Embase	(otosclerosis:ab,ti OR otosclerotics:ab,ti OR otosclerotic:ab,ti OR otospongiosis:ab,ti OR otospongioses:ab,ti OR otospongiotic:ab,ti OR otospongeotic:ab,ti OR stapedotomies:ab,ti OR stapedotomy:ab,ti OR stapedectomies:ab,ti OR stapedectomy:ab,ti OR (stapes:ab,ti AND (surgery:ab,ti OR surgeries:ab,ti OR mobilization:ab,ti OR mobilisation:ab,ti)) OR (ossicular:ab,ti AND (replacement:ab,ti OR replacements:ab,ti))) AND (laser:ab,ti OR lasers:ab,ti OR KTP:ab,ti OR “potassium titanyl phosphate”:ab,ti OR CO2:ab,ti OR “carbon dioxide”:ab,ti OR “Er-YAG”:ab,ti OR erbium:ab,ti OR “yttrium aluminium garnet”:ab,ti OR diode:ab,ti OR argon:ab,ti OR thulium:ab,ti)	Title/ Abstract

Search for studies comparing the effects of lasers, in patients undergoing primary stapes surgery for otosclerosis (date of search: May 22nd 2013).

Assessment of risk of bias involved evaluation of selection bias, notably (1) concealed treatment assignment with random allocation and (2) completeness of reported data; and information bias, notably (3) blinding of treatment nature and outcome assessment, (4) standardization of treatment and (5) standardization of outcome assessment. Studies were classified as having a low risk of bias if they satisfied all of these criteria, moderate risk of bias if they satisfied at least two criteria and the remainder was classified as high risk of bias. When an item of the study assessment was not reported, it was rated ‘unclear’. When an item was reported, it was classified as either ‘satisfactory’ or ‘unsatisfactory’. Initial discrepancies between independent reviewers were resolved by discussion and reported results are based on full consensus. Studies that did not provide direct evidence and/or carried high risk of bias were excluded for further review.

Data extraction – For the included studies, two authors (IW and DK) independently extracted descriptive data of patients and interventions. For the outcomes of interest the absolute risks and their risk differences with the corresponding 95% confidence intervals (95%CIs) were extracted. The primary outcome measure was closure of the air-bone gap to within 10 decibels or less, preferably for the frequencies 500, 1000, 2000 and 3000 or 4000 Hz, which is generally considered a successful outcome of stapes surgery in literature in the sense of the surgeon's surgical performance.[6-8] According to the Committee on Hearing and Equilibrium, follow-up should be at least one year for this outcome measure since results change over time and long-term results provide a more realistic prognosis.[9] Secondary outcome measures were sensorineural hearing loss, vertigo, tinnitus and fractured footplate. Preferably absolute risks were extracted. If these were not given or could not be recalculated, the findings as reported in the article were presented.

Results

Retrieving studies - A total of 1050 titles was retrieved, of which 383 were unique studies (see **Figure 1**; date of last search was May 22nd 2013). After selection based on title and abstract, and subsequent full-text screening, eight articles were initially considered eligible for answering our question.[10-17] Cross-reference checking revealed no additional articles.

Assessing studies - Assessment of their reported methods showed that for seven studies the directness of evidence was high[10-13] or moderate[14-16] (see **Table 2**). For one study the directness of evidence was low.[17] Of these seven studies, one study did not mention whether all patients were treated with primary stapedotomy[16], one study included revision cases as well as patients treated with malleus-to-oval window prostheses[17] and in another study patients were also operated on by residents under close supervision of the senior author.[14] The results of pure-tone audiometry were not reported in one study.[17] Follow up time was only 6-8 weeks in one study[14] or not mentioned.[15] The risk of bias was moderate in four studies[10-12,14] and high in the other four studies[13,15-17]. Adequate randomization, treatment allocation and blinding were either not achieved or no information was provided regarding these criteria. Standardization of treatment was unclear in three of the included studies.[13,16,17] Laser settings were not adequately described in these studies. Standardization of postoperative pure-tone audiometry was achieved in four studies.[10,12,14] For four studies a large amount of outcome data was missing (more than 10%).[10,12,15,17]

Table 2

Study	Sample size of study (n)	Study design	Directness of evidence				Risk of bias					
			Patients	Treatment	Outcome	Directness of evidence	Treatment allocation	Blinding	Standardization (T)	Standardization (O)	Complete data	Risk of bias
Vincent (2012)[10]	839	PCS	●	●	●	H	○	?	●	●	●	M
Marchese (2011)[11]	104	RCS	●	●	●	H	?	?	●	○	●	M
Vincent (2010)[12]	214	PCS	●	●	●	H	○	?	●	●	○	M
Timoshenko(2009)[13]	191	RCS	●	●	●	H	?	?	?	?	●	H
Vernick (1996)[14]	100	PCS	●	●	○	M	○	?	●	●	●	M
Buchman (2000)[15]	87	RCS	●	●	?	M	?	?	●	○	○	H
Szyfter (2012)[16]	142	RCS	?	●	●	M	?	?	?	?	●	H
Antonelli (1998)[17]	38	PCS	○	●	○	L	?	○	?	○	○	H

Study assessment of studies comparing effects of lasers, in patients undergoing primary stapes surgery for otosclerosis

Study Design
RCT = randomized controlled trial; PCS = prospective cohort study; RCS = retrospective cohort study; CS = cohort study, unclear whether in prospect or retrospect; H = high; M = moderate; L = low.

Directness of evidence
Patients: ● = primary stapedotomy for otosclerosis; ○ = primary stapedectomy, revision surgery for otosclerosis, stapes surgery as part of residency training programs, other.
Treatment: ● = at least two lasers for stapedotomy compared; ○ = other.
Outcome: ● = recovery of conductive hearing loss measured by closure of air-bone gap after 3 months or longer; ○ = other.

Risk of bias
Randomization: ● = adequate randomization (e.g. random number table or coin toss); ○ = no adequate randomization (e.g. sequence generated by date of admission or allocation by judgment of clinician); ? = unclear, no information provided.
Treatment allocation: ● = adequate concealment (e.g. sealed envelopes); ○ = no adequate concealment; ? = unclear, no information provided.
Blinding of fenestration method during postoperative pure-tone audiometry and interpretation of audiometry: ● = patients and clinicians blinded; ○ = only patients blinded or no blinding; ? = unclear, no information provided.
Standardization (T) of surgical procedure and laser settings: ● = yes; ○ = no; ? = unclear, no information provided.
Standardization (O) of postoperative pure-tone audiometry with regard to frequencies used and follow-up duration: ● = yes; ○ = no; ? = unclear, no information provided.
Completeness of outcome data for primary outcome: ● = below 10% missing data; ○ = 10% or more missing data; ? = unclear, no information provided.

Five studies with either or both low or moderate directness of evidence and high risk of bias were excluded for further review.[13-17] Furthermore, the study performed by Vincent et al. in 2010[12] was excluded, because all of the patients included in this study were also included in the study performed in 2012 by Vincent et al.[12] Two studies that carried moderate risk of bias were included for further review, all providing evidence of high directness.[10,11,14] Conclusions were based on these two studies.

Data extraction - The extracted data of the included studies are described in **Table 3**. The selected studies included in total 943 procedures. In both of the included studies the CO_2 laser was compared to another type of laser: KTP[10,14] or Er-YAG.[11] There are major dissimilarities between the included studies regarding type of laser, laser settings used and follow-up duration. Not only did fluencies differ across studies, different fenestration techniques were used, namely the rosette and single-shot technique. It needs to be noted that although fluencies used in Er-YAG-assisted stapedotomy are much lower compared to other laser types, multiple shots are needed to create an adequate fenestration.

The extracted outcome data of the included studies are shown in **Table 3**. Risk differences are positive when results favor fenestration by laser II (CO_2 laser in both studies) and negative when results favor laser I (either KTP or Er-YAG). The study comparing KTP and CO_2 laser, performed by Vincent et al. reports a postoperative ABG closure in favor of the CO_2 laser, with a risk difference of 6.1% [95%CI 5.7 , 6.5][10]. In the study performed by Marchese et al.[11], comparing Er-YAG to CO_2 laser, the difference in postoperative ABG closure is in favor of CO_2 laser fenestration as well, with a risk difference of 28.1% [22.8, 33.4].

Sensorineural hearing loss, measured by postoperative bone conduction shift, was evaluated in both studies and did not occur in both study groups.[10,11] Postoperative bone conduction shift was similar for both laser groups in both studies with risk differences of 0.5 [0.5 , 0.5](10) and -1.4 [-1.0 , -1.8].[11]

Other possible side effects of laser fenestration, such as tinnitus or vertigo, were not systematically evaluated in both of the included studies.

Table 3

Study	Laser I (n)	Laser II (n)	Follow-up	ABG closure^ (<10 dB)			Bone conduction shift (dB)		
				Laser I	Laser II	Risk difference (95% CI)	Laser I (mean (SD))	Laser II (mean (SD))	Risk difference (95% CI)
Vincent (2012)[10]	**KTP** (431) 1W, 0.2s, 0.2mm 636 J/cm²	**CO_2** (408) 1.3W, 0.2s, 0.25mm 530 J/cm²	3 months	90.4%	96.5%	6.1% [5.7 , 6.5]	0.8 (5.1)	1.3 (4.6)	0.5 [0.5 , 0.5]
Marchese (2011)[11]	**Er-YAG** (69) 30mJ, 0.38 mm², 0.2ms. 4.6 J/cm²	**CO_2** (35) 20-22W, 0.03-0.05s 0.6-0.8mm 119-389 J/cm²	12-26 months	34.8%	62.9%	28.1% [22.8 , 33.4]	1.6 (7.5)	0.2 (7.9)	-1.4 [-1.0 , -1.8]

Results of studies comparing effects of lasers, in patients undergoing primary stapes surgery for otosclerosis

When risk difference is positive, this favors laser II. When bone conduction (BC) shift is positive, this means BC improved on pure-tone audiometry (PTA) post-operatively. When BC shift is negative, this means BC deteriorated on PTA postoperatively.
n = number of procedures; ABG = air-bone gap; BC = bone conduction; 95% CI = 95% confidence interval; SD = standard deviation; NA = not available.
^ =Closure ABG over 0.5 – 1 – 2 - 4 kHz

Discussion

We included two studies evaluating hearing outcome in laser-assisted stapedotomy, comparing different laser types. The two included studies both carry a moderate risk of bias, while their directness of evidence is high. Both studies show a difference in postoperative air-bone gap closure in favor of CO_2 laser use over the use of KTP or Er-YAG laser. Sensorineural hearing loss did not occur and bone conduction shift was similar for both CO_2 laser and KTP or Er-YAG laser.

The question remains how to interpret these findings. Before generalizing these results into daily clinical practice, there are several things we need to take into consideration. First, all of the identified studies carry moderate to high risk of bias, due to lack of randomization, treatment allocation and blinding of observations and poorly standardized treatment and test procedures. High risk of bias can lead to under- or overestimation of true intervention effects. Second, the included studies differed in their approach to laser settings, expressed in fluencies (J/cm^2), surgical technique, calculation of air-bone gap closure and follow-up duration. Both Vincent et al. and Marchese et al. calculated postoperative air-bone gap closure using postoperative air and bone conduction. According to the Committee of Hearing and Equilibium[9] follow-up of at least one year is preferable when reporting air-conduction thresholds or air-bone gap closure, to ensure the reported outcome is reliable. Vincent et al. has a follow-up of 3 months. Results may change over time and therefore results at one year provide a more realistic representation of hearing outcome than short-term results. Underestimation or overestimation of effects cannot be ruled out when using short-term follow-up. This should be taken into consideration when interpreting the outcome.

Third, differences in hearing outcome when comparing the use of the KTP laser to the use of the CO_2 laser, are small and might not be clinical relevant. Differences between Er-YAG and CO_2 are larger and clinically relevant. Finally, adverse events, such as vertigo or tinnitus, were not systematically evaluated in the included studies. Different lasers have different absorption spectra and therefore it seems likely that occurrence rates of these events would differ between lasers. For instance, we would expect damage to the hair cells as a result of heating of the perilymph in CO_2 laser use or acoustic trauma when using the Er-YAG laser.[4,18-20] Both would result in sensorineural hearing loss in the operated ear. Direct damage to the neuro-epithelium as a result of the use of either KTP or Argon laser, would rather express itself in vertigo.[21] These postoperative side effects should be taken into account when choosing which laser to use, as they can be highly disabling for the patient. Previous patient series have described up to 9% of tinnitus in CO_2 laser use and up to 4% in Er-YAG laser use.[22,23] Even higher percentages of vertigo, up to 20% in Er-YAG and 39% in KTP laser use.[20,24] To adequately compare tinnitus and vertigo complaints in patients, a standardized method of questioning is necessary during the research period.

Conclusion and recommendation

To date, the studies comparing different lasers types used for fenestration in stapedotomy provide only limited evidence. One moderate risk of bias study showed no clinically relevant difference in hearing outcomes when comparing the use of CO_2 laser to the use of KTP laser. One moderate risk of bias study reports a clinically significant difference of 28.1% [22.8 , 33.4] in favor of CO_2 laser, when compared to the use of the Er-YAG laser.
These conclusions are based on a very limited number of studies. Therefore, cost-effectiveness, experience and availability are deciding factors when choosing a laser type to use for stapedotomy. High quality randomized controlled trials or case-control studies should be conducted in order to be able to form firm statements based on higher level of evidence. Hearing outcomes as well as adverse effects, such as postoperative vertigo or tinnitus, should be closely monitored.

Acknowledgements

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4

Comparison of KTP, Thulium and CO_2 laser in Stapedotomy using Specialized Visualization Techniques: Thermal Effects

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Abstract

Hypothesis: High speed thermal imaging enables visualization of heating of the vestibule during laser-assisted stapedotomy, comparing KTP, CO_2 and Thulium laser light.
Background: Perforation of the stapes footplate with laser bears the risk of heating of the inner ear fluids. The amount of heating depends on absorption of the laser light and subsequent tissue ablation. The ablation of the footplate is driven by strong water absorption for the CO_2 and Thulium laser. For the KTP laser wavelength, ablation is driven by carbonization of the footplate and it might penetrate deep into the inner ear without absorption in water.
Methods: The thermal effects were visualized in an inner ear model, using two new techniques: (a) high speed Schlieren imaging shows relative dynamic changes of temperatures up to 2 millisecond resolution in the perilymph. (b) Thermo imaging provides absolute temperature measurements around the footplate up to 40 ms resolution.
Results: The High Speed Schlieren imaging showed minimal heating using the KTP laser. Both CO_2 and Thulium laser showed heating below the footplate. Thulium laser wavelength generated heating up to 0.6 mm depth. This was confirmed with thermal imaging, showing a rise of temperature of 4.7 (+/- 3.5) degrees Celsius for KTP and 9.4 (+/- 6.9) for Thulium in the area of 2 mm below the footplate.
Conclusion: For stapedotomy, the Thulium and CO_2 laser show more extended thermal effects compared to KTP. High Speed Schlieren imaging and thermal imaging are complimentary techniques to study lasers thermal effects in tissue.

Introduction

Stapedotomy is a procedure to improve hearing in patients with otosclerosis. It was introduced as early as the end of the 19th century and many improvements to the technique have been proposed.[1] The most important part of the procedure is the perforation of the stapes footplate, traditionally done by a Skeeter drill or a micro-pick instrument. Possible risks of this direct-contact method, which generates substantial mechanical energy, include sensorineural hearing loss, vertigo and facial nerve paralysis. A non-contact method to perforate the footplate is preferable to minimize these risks. The first non-contact technique was described by Perkins in 1980, using an Argon laser to make a precise hole in the footplate.[2] Up to now, various lasers have been proposed for this cause; however, each has its own characteristics, with the possibility to inflict harm to the inner ear.

Classically used lasers as Argon (488, 513 nm) and KTP (532 nm), bear the risk of damaging the inner ear, due to their light transmission through the perilymph, causing residual energy to be absorbed at the pigmented area of the neuro-epithelium of the vestibule. The pulsed Er-YAG laser (2.94 μm) has the advantage of its high absorption in both fluid and bone, leaving minimal residual energy to enter the vestibule. Nonetheless, the explosive ablation of the bone causes a sound pressure wave, which is considered traumatic to inner ear hear cells, with potential sensorineural hearing loss and vertigo as a result.[3] The CO_2 laser (10.6 μm) (either continuous wave or pulsed) is also well absorbed in both fluid and bone, causing a precise perforation, with the excess of energy being highly absorbed by the perilymph, generating heat[4,5] or a sound pressure wave using short pulses. Although this heat is potentially damaging, the largest disadvantage was the absence a fiber delivery system. Using a micromanipulator coupled to the operating microscope, the beam was focused through the hearing channel onto the footplate. Incorrect alignment of the HeNe-aiming beam, especially in older devices, could result in missing the footplate and harming surrounding structures as the facial nerve.

Recent developments include the introduction of the continuous wave 2 μm laser (usually referred to as Thulium laser) has the advantage of a relative high absorption in water and bone while it can be fiber delivered. Also progress was made in fiber delivery systems for CO_2 lasers based on hollow-wave guides, giving potentially more control for delivery of the laser beam to the footplate.

The aim of this study is to compare the dynamic thermal effects of these different lasers modalities in an inner ear model using a special technique combining high speed and thermal imaging. The optimal laser procedure would preferably inflict minimal temperature increase in the inner ear.

Material and Methods

To study the thermal effects, a special optical technique was used based on color Schlieren imaging.[6] This technique visualizes non-uniformities in the refractive index of a transparent medium induced by e.g. a temperature gradient. Light rays passing through water or a transparent tissue phantom will be deflected if a temperature gradient, caused by laser induced heating, is present. The non-deflected and deflected rays are focused onto a rainbow filter by an imaging lens (**Figure 1**). This produces a colored 'thermal' image showing the presence and dynamics of the temperature gradient in real time (inset **Figure 1**). With a high intensity white illumination source, frame rates up to 500 f/s (= 2 ms resolution) could be obtained. In contrast to a 'standard' thermo camera which can only 'see' surface temperatures at typical 25 f/s (= 40 ms resolution), this technique enables the visualization of temperature effects inside a physiological medium like water and can be combined with a regular high speed camera at high magnification using standard close-up optics. However, it does not show absolute temperatures but rather the relative local temperature dynamics.
For protection of the high speed camera a filter (blocking 530 - 535 nm) was used in the KTP experiments, the maximum frame rate was therefore diminished to 250 f/s.
To visualize effects in the vestibule during perforation of the footplate, experiments were performed on an inner ear model (**Figure 2**). This inner ear model consisted of a slab of transparent polyacrylamide gel sandwiched between 2 glass windows. A 3 mm deep artificial vestibule was created in the gel, corresponding to the depth of a human vestibule. It was filled with NaCl 0.9%, mimicking the perilymph. A small strip of dialysis membrane was placed over the vestibule, with a small hole centrally. A stapes footplate (fresh frozen human cadaver) was placed on top of the hole, so the footplate would make direct contact with the fluid, without sinking. The model was placed in the imaging set-up. The footplate was exposed to the different lasers either with a fiber tip placed directly on the footplate or at 1 mm above. As the KTP wavelength is not absorbed by fluid but by pigmented areas in contrast to the other laser wavelengths used, the polyacrylamide gel was dyed with cherry red colour pigment to mimic absorption effects in the wall of the vestibule.
Absolute temperatures were visualized at the surface of the foot plate using a standard thermo camera (Thermacam TM SC640; FLIR systems). This method cannot be used to thermal effects produced by CO_2 laser light as the 10.6 μm infra-red light will burn the sensors of the thermo camera even at the lowest settings. We placed the footplate in these experiments directly on the polyacrylamide gel, to avoid reflection of infra-red radiation by the glass necessary to contain the water in the vestibule (**Figure 3**).

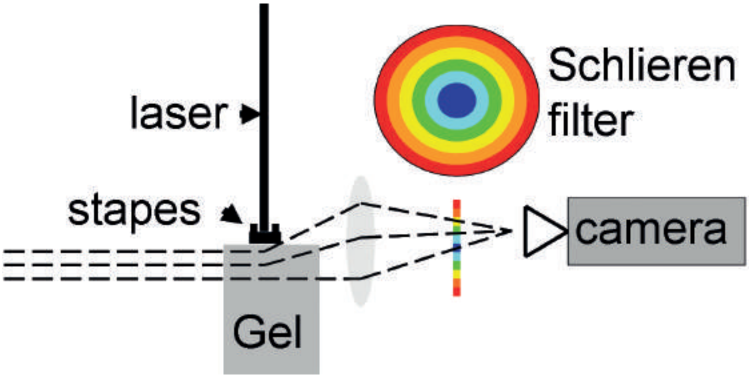


Figure 1 Scheme of the color Schlieren imaging setup

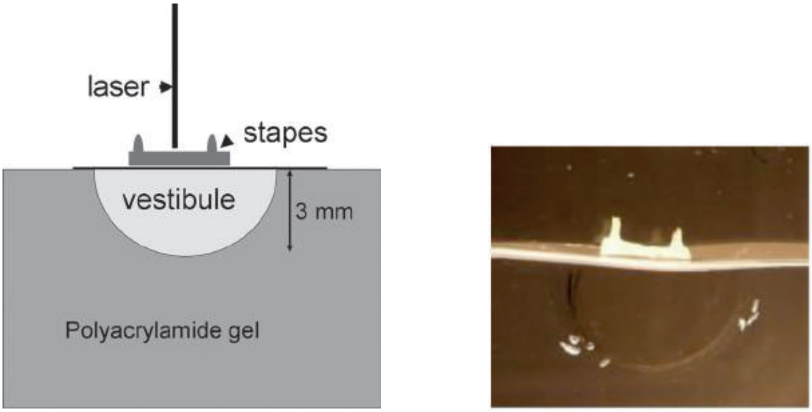


Figure 2 Inner ear model for Schlieren setup. Left (a): schematic setup. Right (b): actual image of model with a stapes resting on a membrane above the vestibule

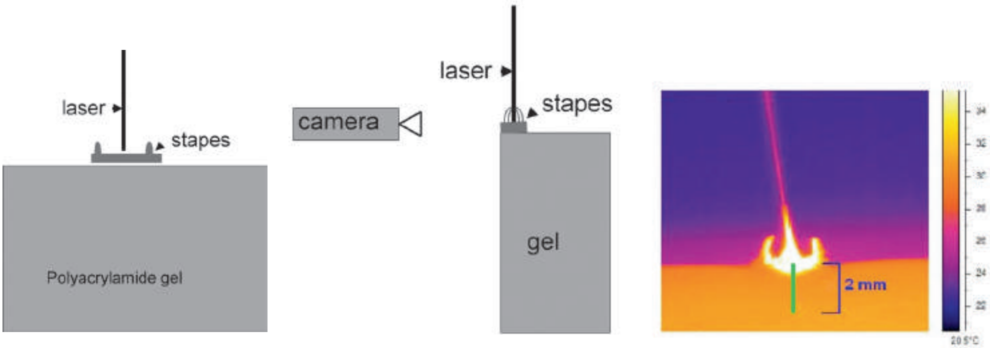


Figure 3 Inner ear model for thermo camera setup. Left (a): schematic setup frontal view as perceived by the camera. Middle (b): schematic setup side view, Right (c): actual imaging by thermo camera. Average heat increase was measured over a 2 mm scope below the foot plate (green line)

chapter 4

The gel was warmed to approximately 30 degrees Celsius (mimicking body temperature) in a small container, before use. Images created with thermo camera were analyzed in a standardized manner. A vertical line was drawn, from the stapes footplate to 2 mm depth (**Figure 3**). At the maximum heat a still image was made, and heating was calculated over the 2 mm course. Minimal and maximal heat was measured over this course with means and standard deviations.

The experiments were performed comparing the following laser systems at settings which are typically used in the clinic as published in literature (see **Table 1**).
A 532 nm KTP laser (IDAS, Quantel Derma, Erlangen, Germany) was used coupled into a fiber hand piece (Endo-ENT, Biolitec, 200 micron). A 2 µm continuous wave ('Thulium') laser was used coupled to a 365 µm fiber. A 10.6 µm continuous wave CO_2 laser (A.R.C. laser, Nurnberg, Germany) was used. The light was delivered by a 3rd generation Omniguide Hollow Wave Guide (Beam-Path OTO-S, 250 µm, Omniguide, Cambridge, MA, USA). A flow of Helium gas was delivered through the center of the fiber (> 1 bar) to prevent pollution of the fiber core.
For each laser setting 3 holes were created in the stapes to confirm reproducibility of the observed effects. The video clips were examine by the authors independently and scored on temperature increase and temperature penetration in the fluid of the vestibule.

Table 1

Laser	Energy output (mJ)	Pulse time (ms)	Spot size (µm)	Fluency (J/cm²)
KTP	100 (at 1 W)	100	200	318
CO_2	200 (at 2 W)	100	250	407
Thulium	600 (at 6 W)	100	365	573

Laser settings shown by energy output (mJ), pulse time (ms), spot size (µm) and fluency (J/cm²)

Results

High Speed Schlieren Imaging

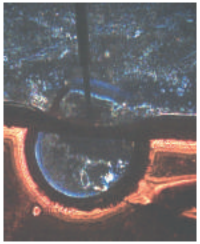
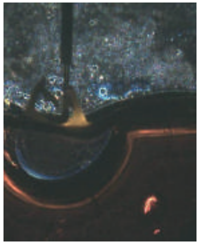
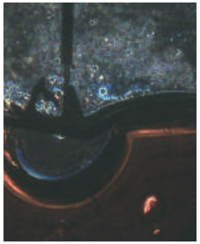
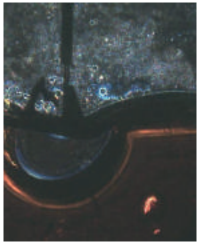
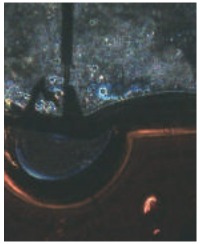
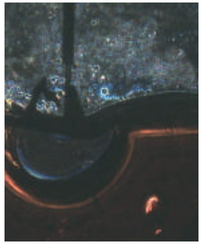
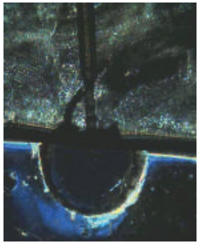
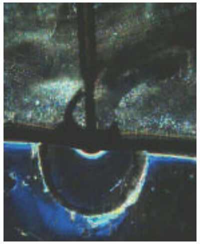
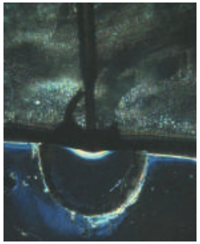
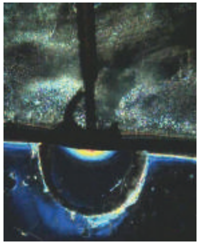
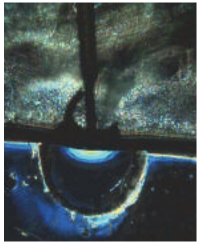
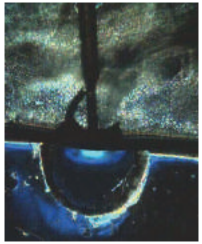
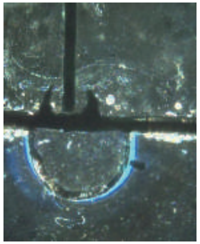
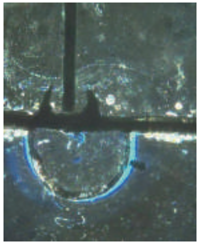
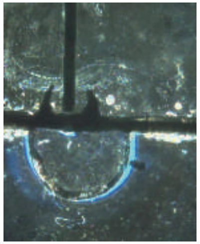
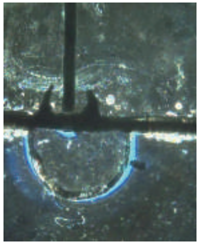
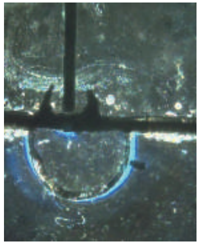
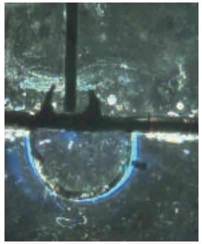
In **Table 2** still frames are shown of the heat distribution during and directly after laser irradiation for the different lasers. The beginning of the pulse is represented by t=0 , t=100ms represents the end of the pulse.

For the KTP laser, the thermal imaging showed a small zone of heated fluid underneath the stapes after perforation. It was expected that excessive energy would not be absorbed in the inner ear fluids, but would be absorbed in pigmented areas, such as neuro-epithelium. To capture this process, in this experiment the gel was dyed with a red color pigment. Even with this pigmentation, no heating of the far wall of the vestibule was observed. (Also see the Video, as Online Resource: Electronic Supplementary Material 1, ESM 1)

With the Thulium laser, more extended thermal effects were observed up to 1 mm below the foot plate. At the end of the laser pulse, already a large area is heated under the foot plate, with a maximum at t=500 ms. The heated area consists of different colored rings representing a steep temperature gradient. (See the Video, ESM 2)

The CO_2 laser light was delivered through a hollow wave guide with the tip positioned ~1 mm above the footplate. After perforation, energy is absorbed in the fluid of vestibule creating vapor bubbles from heated liquid (indicating temperatures > 100 C) in the vestibule, during the pulse (t=100ms). The heating pattern occurs very local, and cools down rapidly (< 1 s). (See the Video, ESM 3)

Table 2

	t= 0 ms start pulse	t= 100 ms end pulse	t= 200 ms	t= 300 ms	t= 500 ms	t= 1000 ms
KTP						
Thulium						
CO_2						

Thermo camera Imaging

Imaging showed more profound heating in the gel below the foot plate with thulium laser, compared to KTP laser. In the course of 2 mm under the foot plate temperatures were analyzed, for each laser (**see table 3**). Each experiment was preformed three times. For the KTP laser, average temperature is 34.7 °C (+/- 3.5 SD). A rise of + 4.7 °C from baseline temperature of 30 °C.

For Thulium laser the average temperature over 2 mm was 39.4 °C (+/- 6.9 SD). The average temperature increase was +9.4 °C. (see the Videos, ESM 4 for KTP and ESM 5 for Thulium)

When plotting temperature changes in time, a strong increase in heating can be seen at 0.6 mm below the foot plate for the Thulium laser (**Figure 4**). The heating also last clearly longer than for the KTP laser. It takes over 4 seconds until the vestibule has cooled down to an acceptable temperature rise of 4 °C. As mentioned in the methods, it was not possible to perform thermo imaging for the CO_2 laser to prevent damage to the camera sensor.

Table 3

Laser	Average change temperature (°C) over 2 mm depth	Standard deviation (°C)
KTP	+4.7	3.5
Thulium	+9.4	6.9

Results for temperature changes and average temperatures measured by thermo camera. Baseline temperature was 30.

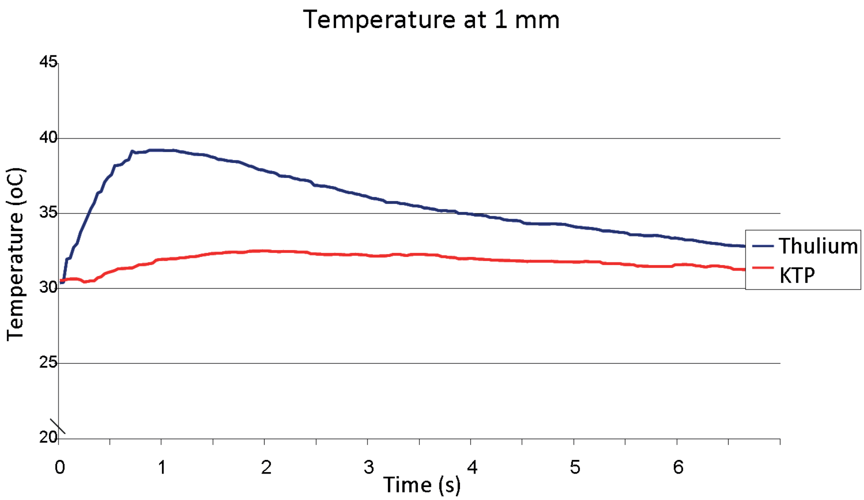


Figure 4 Temperature rise over time, at 1 mm below footplate, for KTP and Thulium laser, measured by thermo camera

Discussion

In this study special imaging were applied to show clearly differences in thermal effects during stapedotomy of the various lasers systems with highest temporal and spatial resolution reported. It is assumed that damage to the inner ear can occur with heating of the inner ear fluids, especially larger rises in temperature or prolonged exposure, leading to vertigo, tinnitus and hearing loss. Our results showed the highest average temperature increase in a region of 2 mm below the footplate of 9.4 °C for the Thulium laser relaxating over 4 s. Also the CO_2 laser showed more thermal effects relative to the KTP laser. Even boiling vapor bubbles were observed.

The highest thermal effect could be expected for the Thulium laser since the energy of 600 mJ in the 100 ms pulse was 6 times higher than KTP and 3 times higher than CO_2. The energy settings were adapted from clinical practice to perforate the footplate effectively (see table 1). The laser effect observed can be estimated considering the volume of tissue that is being heating within the 100 ms pulse. This volume about 20 times larger for Thulium compared to KTP and around 6 times more energy is needed to heat this volume to ablative temperatures. This large hot area was observed with thermal imaging. For KTP the ablation mechanism consist of instant absorption of light by chromaphore in the footplate inducing carbonization that effectively absorbs the light in a layer of tens of microns comparable to the CO_2 laser absorption. Within the 100 ms laser pulse, a canal is drilled through the footplate ending in a none-absorbing liquid showing hardly any thermal effects. The CO_2 laser light will be absorbed by the liquid after footplate fenestration and resulting in heat effects and vapor bubble formation.

The temperature in the original area will drop almost exponentially due to thermal diffusion. At twice the distance from the 'source' the temperature will not exceed 1/8 of the average temperature. The temperature rise of the perilymph volume will be minimal considering the volume in the inner ear.

An overall temperature rise over 4 °C is considered harmful. Animal studies have shown stable inner ear function, up to a 3 °C rise, further heating results in reversible damage and prolonged heating to irreversible changes.[7,8] It can be assumed that that temperature rise of several degrees will result in irreversible damage in humans. So excessive heating during stapedotomy should be avoided. However, the temperature increase observed in this study, even for the Thulium laser, are far below the level where damage is expected. Only when using multiple pulses in a short time, an overall temperature increase in the inner ear might be expected. Only, local temperature rise along the wall of the vestibule might be of concern. However, the distance from the footplate to the wall of the vestibule is above 3 mm and no thermal effects are expected. The hot vapor bubbles induced by the CO_2 laser, will collapse fast with some thermal energy release of which minimal adverse effects can be expected.

Earlier research on heating in the vestibule showed various results. An overview of literature is shown in **Table 4**. Lesinski, Gherini and Kodali used thermocouples to measure heat.[9-11] Outcome measurements differ greatly when using thermocouples. The thermocouples only measures heat at one distinct point, making placement essential. Also size and material of the thermocouple differs the outcome. These limitations make thermocouples not ideal for measuring heat, especially when the area of heating is small and exposure time limited.

Thermal Imaging

A thermo camera captures IR radiation from a surface and absolute temperatures can be deducted. Major advantage to this technique is the possibility to capture the changes of heat for a larger area over time. The drawback to this technique is the inability to measure heat below the surface. Wong used an infrared camera to measure heating of the otic capsule in pigs. He found high rises of temperature in the bone surrounding the perforation site. The question is, how relevant heating of the surrounding bone is, the heating below the footplate in the perilymph is clinically more relevant.

Table 4

	Setup	Laser	Heating
Gardner (1984)[4]	Temporal bone 16 gauge thermocouple central in vestibule	CO_2	+ 1.0 °C
Lesinski (1989)[9]	Inner ear model Black K-type 5 mm thermocouples 2 mm below footplate	KTP CO_2	+ 4.3 °C (KTP) + 0.3 °C (CO_2)
Gherini (1993)[10]	Inner ear model 0.025 mm thermocouples 2 mm below footplate	Argon	No temperature rise
Kodali (1997)[11]	Chinchillas 0.025 mm thermocouple placed in vestibule (through superior canal)	KTP CO_2	+ 2.0 °C (KTP) + 1.8 °C (CO_2)
Wong (1997)[5]	Otic bone of Pig Radial heating of otic bone, measured with thermo camera	KTP CO_2	+ 98 °C, (KTP) + 483 °C (cw CO_2) + 58 °C (SP, CO_2)

Overview of temperature changes in laser assisted stapedotomy in literature

We used a model to measure superficial heating below foot plate in phantom tissue (gel) from the side. Unfortunately, this technique cannot measure heat in liquid directly under the footplate as water itself blocks all IR light. So a detailed imaging of heating processes under the footplate has not been reported yet and seemed impossible.
However, the unique thermal imaging technique presented in this paper, the High Speed Schlieren Technique, enables the imaging of relative temperature changes at high speed. This provides a good insight in the thermo dynamic processes inside the inner ear which give a good prediction of potential damage to inner ear function. With the KTP laser only very locally heating occurs, without any heating of pigmented areas. As the 532 nm green KTP wavelength is not absorbed in water, but in pigmented (blood cells) tissues, it is thought that especially the far wall of the vestibule is at risk to be damaged by irradiation. CO_2 is greatly absorbed in water, showing only minimal penetration of heat in the vestibule using cw laser pulses. Pulsed CO_2 lasers emitting their high intensity pulses of around of several hundred microseconds, can easily create vapor canals through water of centimeters long and damage or even perforate the vestibule on the opposite site. We consider both CO_2 and KTP lasers, with current settings, safe for stapedotomy. Typically, we use these lasers for our primary and revision cases.

As Thulium wavelength is less strongly absorbed in water, more energy is needed to ablate the bone resulting is a larger area of thermal effect as shown with the High Speed Schlieren imaging technique. The results of the Schlieren experiment are supported by the results of the thermo camera. These two techniques combined in our inner ear model, are probable the best available thermo imaging method to provide a good understanding of the dynamics of thermal effects of different lasers and settings in vitro. Measuring the temperature increase of the vestibule during stapedotomy in animals would be the next step as long as it not possible to do it non-invasively in humans. It is well known that beside thermal effects, also mechanical effects are involved especially for shorter laser pulses (<1 ms). Other effects, as noise generation and bubble formation will need to be addressed as well, as they might also cause inner ear damage.

Also new lasers to the field, as the 980 nm Diode laser, should be investigated in more detail. The effects of this wavelength should mimic KTP laser. As the Diode laser is small and relatively inexpensive, it could be an interesting laser for fenestration. These experiments are work in progress.

In conclusion we showed comparative thermal effects and absolute temperature increases inside the vestibule for KTP, CO_2 and Thulium laser in stapedotomy, using special visualization techniques. Thulium laser showed relative more thermal effects, potentially harming inner ear function.

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chapter

4

5

Comparing Mechanical Effects and Sound production of KTP, Thulium and CO_2 laser in Stapedotomy

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Abstract

Hypothesis: The mechanical and acoustic effects that occur during laser-assisted stapedotomy differ among KTP, CO_2 and Thulium lasers.

Background: Making a fenestration in stapedotomy with a laser minimizes the risk of a floating footplate caused by mechanical forces. Theoretically, the lasers used in stapedotomy could inflict mechanical trauma due to absorption in the perilymph, causing vaporization bubbles. These bubbles can generate a shock wave, when imploding.

Methods: In an inner ear model, we made a fenestration in a fresh human stapes with KTP, CO_2 and Thulium laser. During the fenestration we performed high-speed imaging from different angles, to capture mechanical effects. The sounds produced by the fenestration were recorded simultaneously with a hydrophone; these recordings were compared to acoustics produced by a conventional microburr fenestration.

Results: KTP laser fenestration showed little mechanical effects, with minimal sound production. With CO_2 laser, miniscule bubbles arose in the vestibule; imploding of these bubbles corresponded to the acoustics. Thulium laser fenestration showed large bubbles in the vestibule, with a larger sound production than the other two lasers. Each type of laser generated significantly less noise than the microburr. The microburr maximally reached 95 ± 7 dB(A), compared to 49 ± 8 dB(A) for KTP, 68 ± 4 dB(A) for CO_2 and 83 ± 6 dB(A) for Thulium.

Conclusion: Mechanical and acoustic effects differ among lasers used for stapedotomy. Based on their relatively small effects, KTP and CO_2 lasers are preferable to Thulium laser.

Introduction

Stapedotomy is a procedure to improve hearing in patients with a conductive hearing loss due to otosclerosis. It was introduced as early as the end of the 19^{th} century and many improvements to the technique have been proposed.[1] One of the most important steps of the procedure is the perforation of the stapes footplate, traditionally done with a micropick instrument and later with a microburr. Possible risk of these direct-contact methods, due to mechanical forces, is the occurrence of a floating footplate or inner ear trauma.[2] This can result in substantial sensorineural hearing loss and vertigo. Therefore, a non-contact method to perforate the footplate is preferable. The first non-contact technique was described by Perkins in 1980, using an Argon laser to make a precise hole in the footplate.[3] However, using lasers to perforate the footplate is not without risks. The classically used lasers as Argon (488 nm) and KTP (532 nm), bear the risk of damaging inner ear structures, as residual energy is absorbed in pigmented areas in the vestibule.[4] CO_2 (10.6 μm) and Thulium laser (continuous wave 2 μm) are strongly absorbed in water, causing heating of the perilymph.[5-8] It is thought that heating of the inner ear fluids can cause vertigo, tinnitus and/or hearing loss, either temporary or permanent.[9-11] Recent thermal high speed imaging confirmed heating by CO_2 and Thulium laser.[8]

chapter 5

Besides heating, also mechanical and acoustic effects can occur during laser-assisted stapedotomy. These effects are mainly caused by absorption of laser energy in water. During this fast absorption, especially in pulsed-laser systems in the mid-infrared region, vapor bubbles can arise.[12-15] Fast expansion of the vapor and especially the implosion after cooling of the vapor, may generate substantial pressure waves and acoustic shock waves.[16,17] These effects could be traumatizing to the fragile inner ear structures. Whether these effects occur with the lasers currently used for stapedotomy has not been investigated yet. We performed high-speed imaging, while concurrently recording sound production, to capture both the mechanical and acoustic effects. The mechanical effects during perforation occur in milliseconds. It is difficult to capture this using regular imaging. High Speed Imaging has the advantage of capturing effects which are invisible to the human eye. A better insight in these effects might help us to make the right choice which type of laser and which settings to use in stapedotomy.

Material and Methods

Inner ear model

To visualize effects in the vestibule during perforation of the footplate, experiments were performed on an inner ear model (**Figure 1**). This inner ear model consisted of a slab of transparent polyacrylamide gel sandwiched between 2 glass windows. Half of a hole was punched in the gel, creating a 3 mm deep artificial vestibule, corresponding to the depth of a human vestibule. The cylindrically shaped vestibule was filled with NaCl 0.9%, mimicking the perilymph. A small strip of dialysis membrane was placed over the vestibule, with a small hole centrally. A stapes footplate (fresh frozen human cadaver) was placed on top of the hole, so the footplate would make direct contact with the fluid. The model was placed in the imaging set-up. All experiments took place at room temperature. The footplate was exposed to the different lasers either with a fiber tip placed directly on the footplate or at 1 mm above. No more than 4 holes were created per stapes. We used a total of 20 stapes throughout the experiments.

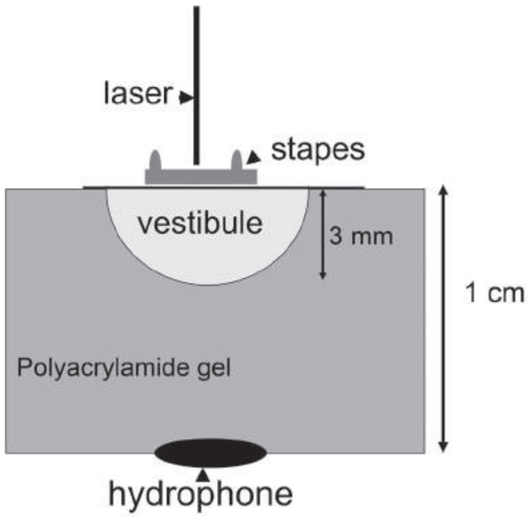

Figure 1 Inner ear model as seen by the high speed camera in "perpendicular" angle. The inner ear model consists of a polyacrylamide gel with an artificial vestibule, a fresh frozen human stapes and a laser fiber. Hydrophone is placed 1 cm below the stapes footplate. This model was contained in a glass container and placed in the image setup

Laser systems

The experiments were performed comparing the following laser systems at settings which are typically used in the clinic as published in literature (see **Table 1**). Single pulses of 100 ms are used. A 532 nm KTP laser (IDAS, Quantel Derma, Erlangen, Germany) was used coupled into a fiber hand piece (Endo-ENT, Biolitec, 200 micron). A 2 μm continuous wave ('Thulium') laser (LISA laser, Katlenburg, Germany) was used coupled to a 365 μm fiber. A 10.6 μm continuous wave CO_2 laser (A.R.C. laser, Nurnberg, Germany) was used. The light was delivered by a 3rd generation Omniguide Hollow Wave Guide (Beam-Path OTO-S, 250 μm, Omniguide, Cambridge, MA, USA). A flow with helium gas was delivered through the center of the fiber (> 1 bar) to prevent pollution of the fiber core.

Table 1

Laser	Energy output (mJ)	Pulse time (ms)	Spot size (μm)	Fluency (J/cm^2)
KTP	100 (at 1 W)	100	200	318
CO_2	200 (at 2 W)	100	250	407
Thulium	600 (at 6 W)	100	365	573

Laser settings shown by energy output (mJ), pulse time (ms), spot size (μm) and fluency (J/cm^2)

High speed imaging

The stapes in the inner ear model was placed with the laser in the imaging set-up. With the high speed camera images were made from two distinct angles. 'Perpendicular' images, perpendicular to the footplate, were done to capture the effects under the footplate. The 'above' imaging, was made with a 20 degrees oblique view from the top. From this angle the effects above the stapes and the creation of the fenestration can be visualized. With a high intensity white illumination source, frame rate up to 4000 f/s (= 250 μs resolution) could be obtained. For protection of the high speed camera a filter (blocking 530-535 nm) had to be used in the KTP experiments. For each laser setting 3 holes were created in the stapes to confirm reproducibility of the observed effects. The video clips were examined by two authors (DK and TdB) and scored on particle, plume and bubble formation.

Acoustic Measurements

The sound production was measured by a hydrophone (Kingstate, Omni, sensitivity -42 ± 3dB, maximum frequency range 25-20000 Hz, diameter 6 mm), located 1 cm below footplate. Recordings were made during 100 ms after onset of the laser pulse. The hydrophone was calibrated with a reference source (Blaupunkt speaker, PCxb352) presenting pure tones over the whole frequency range (125 Hz – 16 kHz) at 10 cm distance from the hydrophone. Sound levels were determined with a sound level meter (Brüel & Kjær, 2203) and a 1 inch microphone (Brüel & Kjær, 4132).

For each laser fenestration a 100 ms audio clip was recorded. The data was analyzed using custom-written software in Matlab® 7.6 (the Mathworks, Inc) programming environment. Within the raw data, the 10 ms with highest amplitudes were analyzed. Over this time frame a frequency analysis was performed (Fourier analysis), breaking the signal into 1/3-octave bands. The peak frequency, i.e. the frequency with the highest sound level, was identified. The level of this peak was converted into dB(A). This A-weighting makes it possible to identify the damaging characteristics of a sound, according to its frequency, as the ear is not equally sensitive for all frequencies. Therefore, the conversion to dB(A) makes it possible to compare the potential harm of the sound produced by these lasers. For each laser at least 10 recordings were performed to ensure reproducibility.

The sound recordings of the laser experiments were compared to the sound production of an Osseostap microburr, 8 mm diamond drill (Bien-Air, Bienne, Switzerland). In these experiments the stapes was directly placed on the polyacrylamide gel and fixed between three pin needles. Without fixation the stapes footplate tends to start to spin with the rotating drill. As the drill needs time to speed up, timeframe of measurement was prolonged to 1 second. Other test settings remained stable between the experiments.

The results of all these recordings were analyzed per laser group. Statistical analyses were performed by means of repeated-measures analysis of variance (rm ANOVA), using SPSS for Windows (version 20.0). Effects were considered statistically significant for p-value of <0.05.

Results

High speed Imaging

In **Figures 2, 3 and 4** snapshots of the high-speed videos are shown at different times during footplate perforation. Moment t=0ms represents the beginning of the laser pulse, t= 100 ms the end of the pulse. All High Speed Videos are available on the website as Supplemental Digital Content (SDC).

Notably the KTP laser suffers from a large area of carbonization at the fiber tip (indicated by the white arrow in Fig. 2). No particles enter the vestibule during perforation. The tip of the fiber and the stapes bone emit light during the laser pulse. This phenomenon occurs with high temperatures, of over 300 °C. These high temperatures cause dehydration of the bone and direct carbonization. After the single laser pulse, around 200 ms, a small cloud of debris or micro particles arises in the middle ear, indicated by the green arrows in figure 2. Finally a small, conical hole arises in the footplate with a large carbonized formation (**Figure 2**, SDC1 and 2.)

During the CO_2 laser pulse, miniscule gas bubbles are pushed into the vestibule, due to fast absorption of the relatively long CO_2 wave (10.6 μm) in the perilymph (red arrows, **Figure 3**). These bubbles generated small pressure waves, which could be identified in the sound recordings (see below). A small cloud of debris (green arrow, **Figure 3**) arises from the footplate, less dense than the cloud seen with the KTP laser. Like KTP, the final hole is conical, with a large carbonized rim (**Figure 3**, SDC 3 and 4).

Thulium laser shows large effects in both vestibule and middle ear, without the creation of a nice perforation hole. The fiber tip emits light, indicating it reached temperatures of over 300 °C. It causes dehydration of the stapes bone, with carbonization. In the vestibule larger vaporization bubbles arise (red arrows, **Figure 4**), even when the footplate appears to be totally intact. After the laser pulse a large area of very thin bone appears to be created, without a clear perforation. The bone has become very fragile; with minimal manipulation a hole can be created. When accidentally firing another shot at the same place, even larger bubbles arise below the footplate. A small plume of particles is marked by the green arrow (**Figure 4**, SDC 5 and 6).

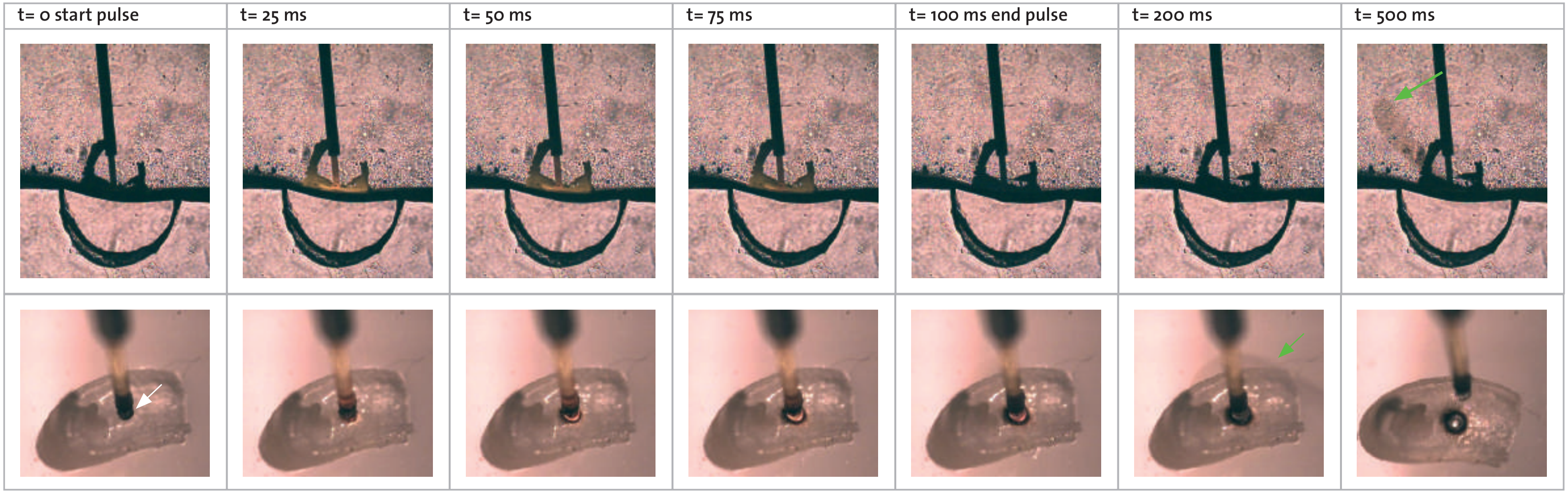

Figure 2 KTP
High Speed Imaging: snapshots at 0, 25 , 50 , 75 , 100 , 200 and 500 ms. t= 0 represents beginning of the single laser pulse, 100 ms the end of the pulse. On the top the "perpendicular" view, on the bottom the view from "above". Green arrows indicate plume of particles. White arrow indicates the carbonization of the fiber tip. (See the videos, Supplemental Digital Content, SDC1 and SDC2).

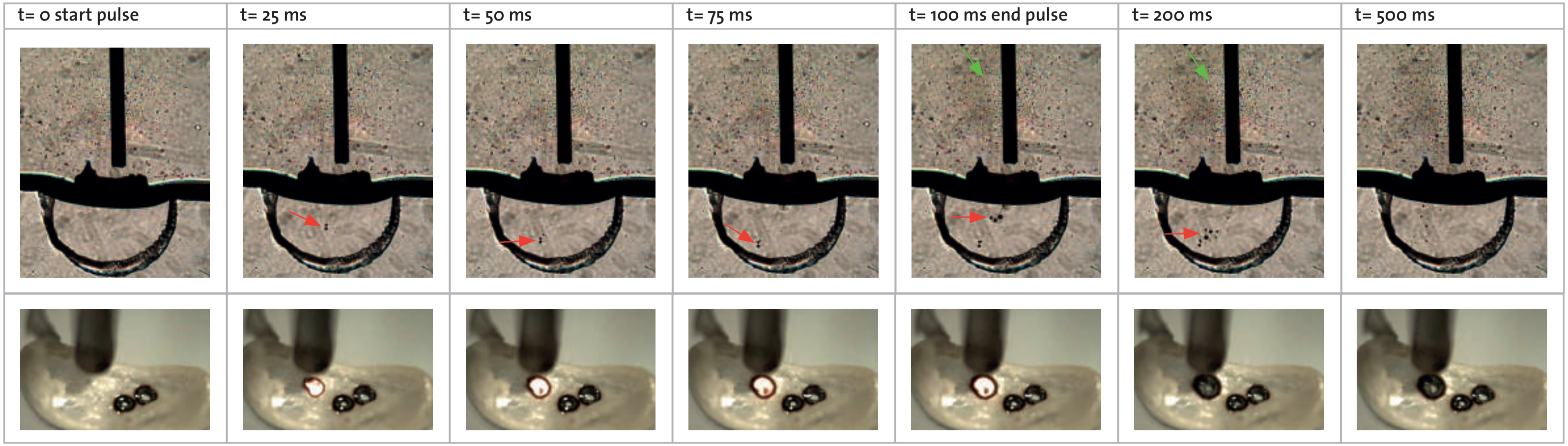

Figure 3 CO2
High Speed Imaging: snapshots at 0 ,25 , 50 , 75 , 100 , 200 and 500 ms. t= 0 represents beginning of the single laser pulse, 100 ms the end of the pulse. On the top the "perpendicular" view, on the bottom the view from "above Green arrows indicate plume of particles. Red arrows indicate bubbles arising in the vestibule. (See the videos, Supplemental Digital Content, SDC3 and SDC4).

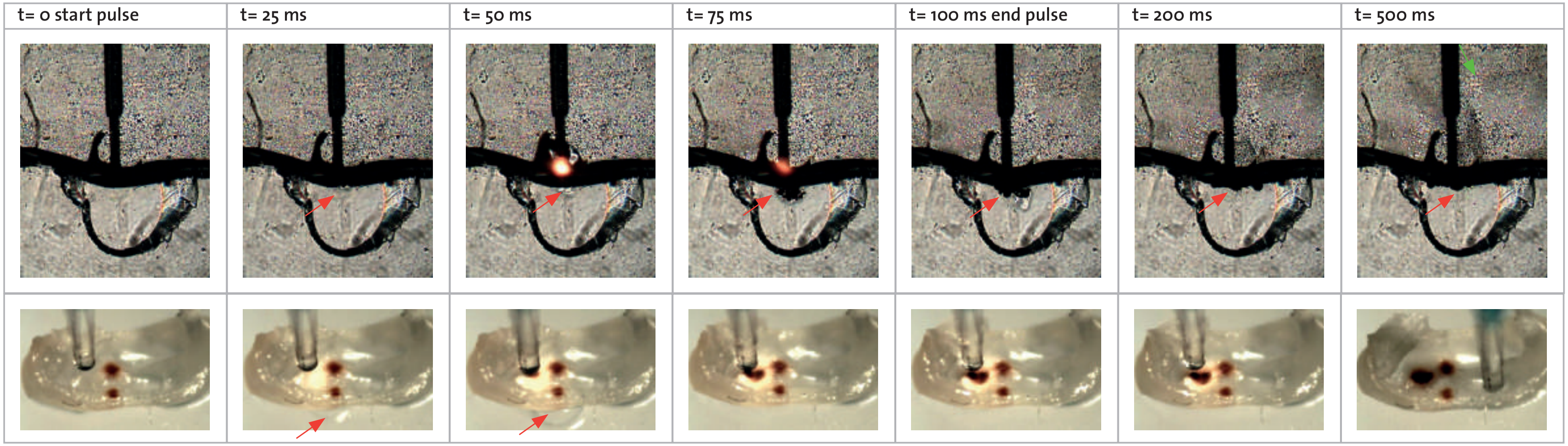

Figure 4 Thulium
High Speed Imaging: snapshots at 0 ,25 , 50 , 75 , 100 , 200 and 500 ms. t= 0 represents beginning of the single laser pulse, 100 ms the end of the pulse. On the top the "perpendicular" view, on the bottom the view from "above Green arrow indicates plume of particles. Red arrows indicate the bubbles entering the vestibule. (See the videos, Supplemental Digital Content, SDC5 and SDC6).

Acoustic measurements

The sound generated by the laser pulse perforation, differs greatly among the three types of laser. The raw recordings show that the KTP produces most noise in the first 20 ms after pulse onset, the CO_2 produces peaks during the entire 100 ms interval, and the Thulium produces a sound that gradually dampens (**Figure 5**). Analysis of the sounds was done within the 10 ms with highest amplitude. Fourier analysis of this peak period revealed the 1/3 octave bands that contributed most to the sound. Remarkably, the KTP produced mainly low frequencies (around 100 Hz). CO_2 and Thulium generated noise with a wider frequency range peaking around 1-2 kHz. The noise of the microburr was in a narrow range around higher frequencies (2-3 kHz).

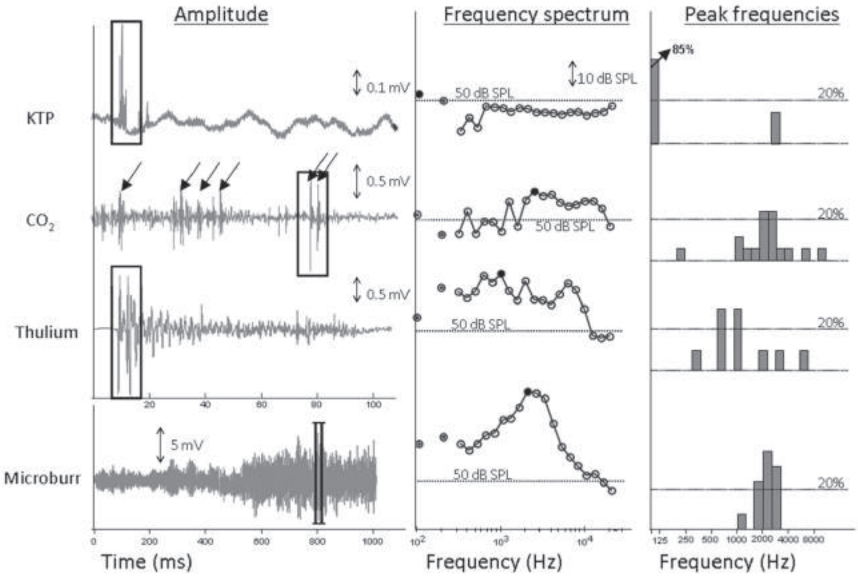

Figure 5 Acoustic measurements
On the left side an example of a raw audio recording for each laser. Over the time frame of 10 ms with largest amplitudes (box), a frequency spectrum was obtained. This frequency spectrum is shown with a reference line of 50 dB SPL in the central column. Of each spectrum the peak frequency was located (black dot). In the right panel the peak frequencies were shown for all the measurements taken. Laser data are compared to audio recordings of the microburr.
Black arrows in CO_2 indicate the pressure waves, corresponding to the bubbles arising in the vestibule and imploding of these bubbles (see figure 3, SDC3)

All lasers generated substantially less noise than a drill, as shown in **Figure 6.** The microburr maximally reached 95 ± 7 dB(A), compared to 49 ± 8 dB(A) for KTP, 68 ± 4 dB(A) for CO_2 and 83 ± 6 dB(A) for Thulium. These differences are statistically significant as determined by one-way Anova ($p<0.001$). A Bonferroni post-hoc test revealed that all lasers and microburr significantly differ from each other in noise production ($p<0.001$).
When looking more into detail at the acoustic signal of the CO_2, we can identify small shockwaves. Comparing the sounds to the high speed imaging, we can correlate the moments the amplitude is rising, to the moments bubbles arise and implode in the vestibule. These pressure waves might also be present in the Thulium acoustic measurement, but can be less clearly seen, as the overall level of sound production is higher. The pressure waves might be hidden within the signal.

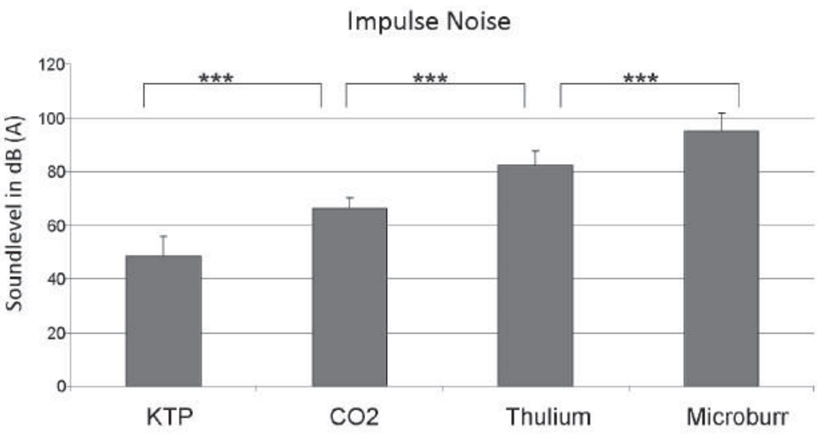

Figure 6 Sound production by laser and drill in dB(A)
Sound production calculated over the 10 ms with highest amplitude. With Fourrier analysis the peak frequency was identified. Pressure levels were converted to dB(A).
Error bars present standard deviations. *** p<0.001

Discussion

The main surgical goal of a stapedotomy is air-bone conduction closure without complications. Unwanted side effects of the surgical technique, as vertigo, sensorineural hearing loss and tinnitus are thought to be inflicted by trauma to the inner ear structures. Previous research has focused on thermal effects in the inner ear, which appear to be small for most lasers.[6,8,11,18,19] Comparing the same lasers in high speed Schlieren imaging, visualizing heating patterns in the vestibule, we found that Thulium laser generates most heating.[8] In our present study, we have clearly shown differences in mechanical and sound effects occurring around the footplate. With the KTP laser the effects appear to be small, although the plume of smoke in the middle ear is largest compared to the other lasers. Probably this plume will not create damage to the inner ear. The continuous wave CO_2 laser can be a good alternative to KTP, even more now that fiber delivery is possible. The CO_2 wavelength cannot be delivered by silica fibers, therefore a hollow wave guide was developed.[20] To prevent damage to the core, 1 bar helium is sent through the fiber. Theoretically this air flow might result in particles of char being pushed into the vestibule. Or more risky, helium gas can be blown into the vestibule when the fiber makes uncontrolled contact with the footplate. This was not seen in our imaging.

We did see small vaporization bubbles being pushed into the vestibule, matching pressure waves seen in the sound recordings. The clinical relevance of these bubbles remains unclear. Animal studies with CO_2 laser show steady hearing after laser irradiation, however some damage to inner and outer hair cells at higher laser fluencies is reported.[4,21,22] It is known that in a closed space, bubble formation is less likely.[12] However, bubbles will only occur at high pressure, inducing small explosions and implosions that can be damaging. The heating of the fluid will result in a small expansion of volume, inducing pressure waves in lower frequencies when compared to bubble dynamics. One should consider here a limitation of our inner ear model: the gel surrounding the artificial vestibule is more flexible than the bony covering of actual inner ear organs. As a result, on the one hand the model possibly overestimates the occurrence of the microbubbles, since the bubbles will be more easily produced when fluid in the vestibule can expand. On the other hand, the model may underestimate the pressure waves, since the waves that occur as a result of implosion of the bubbles, might be more dampened due to the flexible borders. The net effect of the larger flexibility of the model is not clear.

Thulium laser shows largest effects in the vestibule, ironically occurring when the footplate seems to remain intact. The thulium 2 μm wavelength seems to have a less bone ablating effect. The light is partially transmitted through the bone and preferentially absorbed by the water content. The water is vaporized while the bone structure remains

intact and becomes porous, rather than making a clear perforation. In the vestibule larger bubbles arise, which may put the inner ear structures at risk. We observed even a stronger effect, when shooting twice in the same location, when no apparent perforation was observed. In the human situation numerous laser shots are needed to create a rosette of a size of 0.5-0.7 mm. Therefore, risk of larger bubble formation is apparent.
The perforation created with the lasers differs among the three types. Ideally a straight hole would be created, not conical, without excessive carbonization in the borders. Smooth edges of the perforations might result in better movement of the piston in the hole, with a better air-bone conduction closure. None of these lasers show these properties, but in a comparable study between KTP and CO_2 laser, better closure was seen at 4 kHz for CO_2 laser.[23]
The sound production also differs among the lasers (**Figures 5, 6**), although all lasers generate significant less noise than a conventional microburr. Animal research on impulse noise has shown that a temporary threshold shift can occur with impulse noises over 110 dB. With rapid, multiple, repetitions these temporary threshold shifts can become permanent.[24] In humans the sensitivity for impulse noises differs greatly between individuals, making it difficult to predict outcome.[25] The impulse noise of the lasers seems small and clinically irrelevant. But we should take into consideration the close relation of the inner ear and the source of sound. There is no protective mechanism (i.e. stapedial reflex) in place during stapedotomy, to prevent the pressure waves to enter the inner ear. More understanding how these pressure waves are generated and interact with surrounding tissue is needed to predict possible harming characteristics of these impulse noises. A possible way to gain this information might be to visualize these pressure waves, using high speed imaging techniques.

In conclusion, mechanical and acoustic effects differ between lasers used for stapedotomy. With high speed imaging bubble formation can clearly be visualized in CO_2 and Thulium laser fenestration. These bubbles can cause small pressure waves, which we could locate in our sound recordings. All lasers generate less sound than a conventional microburr. For laser stapedotomy the KTP and CO_2 lasers are preferable to the Thulium laser.

Acknowledgements

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chapter

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6

Capturing Thermal, Mechanical and Acoustic effects of the Diode (980 nm) Laser in Stapedotomy

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Otol Neurotol. 2014;35:1070-1076

Abstract

Introduction: The Diode laser, with a wavelength of 980 nm, has promising characteristics for being used for the fenestration during stapedotomy. It is known that at this wavelength absorption in pigmented tissues is high and absorption in water is relatively low compared to medical lasers in the infrared, making it theoretically an applicable laser for stapes surgery in patients with otosclerosis. Another important advantage is that, with respect to other lasers, this device is relatively inexpensive. Despite the potential advantages, the available literature only shows limited reports of this laser being used in stapes surgery. The present paper evaluates the thermal, mechanical and acoustic properties of the Diode laser during stapes surgery.

Methods: For the mechanical effects, high speed imaging with a frame rate up to 4000 f/s (= 250 µs resolution) was performed in an inner ear model. For thermal effects the high speed Schlieren technique was used. Acoustics were recorded by a hydrophone, incorporated in the model. Pulse settings were 100 ms, 3W, which are the same settings used during stapes surgery.

Results: The application of the Diode laser resulted in limited mechanical and thermal effects. Impulse noise was low with an average of 52 (SD 7.8) dB (A). Prior carbonization of the tip of the delivery laser fiber enhances ablation of the footplate.

Conclusion: The 980 nm Diode laser is a useful tool for laser-assisted stapedotomy in patients with otosclerosis. Mechanical, thermal and acoustic effects are limited and well within the safety limits.

Introduction

Argon laser stapedotomy was first introduced by Perkins in 1980.[1] Performing the fenestration of the footplate with a laser has proven to be safer than the use of traditional instruments.[2] Until now, various lasers have been proposed to be safe for use in stapedotomy. However, each of these lasers has its own specific characteristics which influence its potential risk to damage the inner ear structures.

The traditionally used lasers, such as the Argon (488 nm) and KTP (532 nm) laser, bear the risk of damaging the inner ear. Due to their light transmission through watery liquids, such as the perilymph, unwanted energy is absorbed at the pigmented area of the neuro-epithelium of the vestibule. The pulsed Er-YAG laser (2940 nm) ablates bone with explosions, causing a sound pressure wave, which is considered potentially traumatic to inner-ear hair cells by some surgeons.[3,4] The CO_2 laser (10600 nm), used in both continuous wave and pulsed wave mode, is well absorbed in both fluid and bone, causing a controlled perforation. Excess energy is highly absorbed by the perilymph and therefore will not reach the neuro-epithelium.[5,6] Recently hollow waveguides have been introduced for CO_2 lasers: instead of delivering the CO_2 laser beam as a free beam through an articulated arm, the beam is transmitted through a flexible hollow air core fiber. Waveguides allow direct delivery of energy to the tissue. Drawbacks are the costs of these systems and the fragility of the somewhat bulky fiber.

The first report in the ENT literature of the Diode laser was in 2000.[4] The Diode laser consists of a semiconductor device, producing coherent radiation in the infrared spectrum. Due to its high efficiency, it can generate high-energy output while limited energy is supplied. Even small, battery-powered, hand-held devices can produce the necessary energy fluences. The 800 to 1064 nm wavelengths are most commonly used in medical practice and can be easily fiber delivered. Absorption characteristics include high absorption in pigmented tissues and low absorption in water compared to the CO_2 and Er-YAG laser. Compared to KTP laser it has much higher absorption in water. These characteristics potentially make it a suitable laser for otosclerosis surgery. After fenestration of the footplate part of the excessive energy will be absorbed in the perilymph. The remaining energy will be absorbed in the pigmented region of the neuro-epithelium, although it is much less compared to the Argon and KTP-laser [7]. Current applications of the Diode 980 nm laser include hair removal, treatment of port wine stains and treatment of epistaxis in selected cases.[8-10]

The aim of this study is to investigate the thermal, mechanical and acoustic effects of the Diode laser, with a wavelength of 980 nm, in an inner ear model.

Material and Methods

Inner ear model

To visualize the effects in the vestibule during perforation of the footplate, experiments were performed in an inner ear model. A schematic drawing of the inner ear model used for our experiments is shown in **Figure 1**. A slab of transparent polyacrylamide gel was sandwiched between 2 glass windows. These glasses are tightly slid in a plastic holding container. A 3 mm deep artificial vestibule was created in the gel, corresponding to the depth of the human vestibule. The artificial vestibule was filled with NaCl 0.9%, mimicking the perilymph. A NaCl solution was used, since it has the same light absorption properties as perilymph. A small strip of dialysis membrane, with a small central perforation, was placed over the artificial vestibule. A fresh frozen human cadaver stapes footplate was placed directly on top of the perforation in the dialysis membrane, thereby ensuring that the footplate is in direct contact with the fluid. The dialysis membrane keeps the footplate from sinking. No more than 4 perforations were made per stapes (not overlapping) and a total of 10 stapes were used. The model was placed in the imaging set-up. All tests were done in room temperature. The fiber tip of the Diode laser was placed directly onto the footplate before firing the laser.

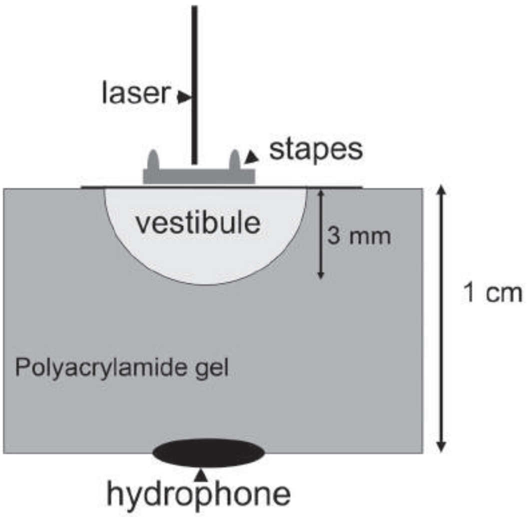

Figure 1 Inner ear model as seen by the high speed camera in "perpendicular" angle. The inner ear model consists of a polyacrylamide gel with an artificial vestibule, a fresh frozen human stapes and a laser fiber. Hydrophone is placed 1 cm below the stapes footplate. This model was contained in a glass container and placed in the image setup

Mechanical effects

Mechanical effects as a result of perforation occurred within the first milliseconds following the laser pulse. The frame rate of conventional imaging is not sufficient to register the effects that occur in a time frame this small. Therefore, high speed imaging was used instead. Using a high intensity white illumination source, a frame rate of 4000 frames per second (f/s) (= 250 μs resolution) was obtained. Furthermore, high speed imaging allowed us to use different viewing angles and capture processes occurring around the footplate and in the vestibule. For each laser setting 3 holes were created in the stapes to confirm reproducibility of the observed effects. The video clips were examined by two authors (DK and TdB) and scored on particle, plume and bubble formation.

Thermal effects

A special optical technique based on color Schlieren imaging was used to study the thermal effects.[11,12] This technique visualizes inhomogeneities in the refractive index of a transparent medium induced by, for example, temperature gradients. Light rays passing through water or a transparent tissue phantom will be deflected when a temperature gradient, caused by laser-induced heating, is present. The undeflected and deflected rays are focused onto a rainbow filter by an imaging lens. This produces a colored 'thermal' image showing the presence and dynamics of the temperature gradient in real time. These 'thermal' images do not show absolute temperatures, but rather the relative local temperature dynamics. Using a high intensity white illumination source, frame rates up to 1000 f/s (at 1 ms resolution) were obtained. In contrast: a 'standard' thermal camera can only typically detect surface temperatures at a frame rate of 25 f/s (at 40 ms resolution). This technique also enables the visualization of temperature effects inside a physiological medium like water and can be combined with a regular high speed camera at high magnification using standard close-up optics. The same test set-up was previously described and used to visualize thermal effects of the KTP, CO_2 and Thulium laser.[12]

A camera filter was used during the experiments to protect the high speed camera, as video cameras are highly sensitive for the infrared light. Three fenestrations were created in the stapes to confirm reproducibility of the observed effects. The video clips were examined and ranked independently by two of the authors (DK, TB), after which results were compared. Discrepancies between independent rankers were resolved by discussion and reported results are based on full consensus. In this article, video stills will be represented of the imaging obtained. The High Speed Imaging Videos will be accessible online as Supplemental Digital Content (SDC).

Acoustic effects

The sound production was measured by a hydrophone (Kingstate, Omni, sensitivity -42 ± 3dB, maximum frequency range 25-20000 Hz, diameter 6 mm), which was placed 1 cm below the stapes footplate.

Recordings were made during 100 ms after onset of the laser pulse. The hydrophone was calibrated with a reference source (Blaupunkt speaker, PCxb352) presenting pure tones over the whole frequency range (125 Hz – 16 kHz) at 10 cm distance from the hydrophone. Sound levels were determined with a sound level meter (Brüel & Kjær, 2203) and a 1 inch microphone (Brüel & Kjær, 4132). For each laser fenestration a 100 ms audioclip was recorded. The data was analyzed using custom-written software in Matlab® 7.6 (the Mathworks, Inc) programming environment. Within the raw data, the 10 ms with highest amplitudes were analyzed. Over this time frame a frequency analysis was performed (Fourier analysis), breaking the signal into 1/3-octave bands. The peak frequency, i.e. the frequency with the highest sound level, was identified. The level of this peak was converted into dB (A). This A-weighting makes is possible to identify the damaging characteristics of a sound, according to its frequency, as the ear is not equally sensitive for all frequencies. Converting to dB(A) makes it possible to compare the potential harm of the sound produced by different lasers.

In a previous experiment, a 532 nm KTP laser (IDAS, Quantel Derma, Erlangen, Germany), a 2 µm continuous wave ('Thulium') laser (LISA laser, Katlenburg, Germany) and a 10.6 µm continuous wave CO_2 laser (A.R.C. laser, Nurnberg, Germany) were already tested. Settings were conform clinical practice; KTP 1W, 100 ms, fiber 200 micron; Thulium 5W, 100ms, 372 micron fiber; CO_2 2W, 100 ms, 250 nm hollow wave guide. A flow with Helium gas was delivered through the center of the hollow wave fiber (> 1 bar) to prevent pollution of the fiber core. All lasers were tested in the same testing paradigm as the Diode laser.

The results of all these recordings were analyzed per laser group. Statistical analyses were preformed by means of repeated-measures analysis of variance (rm ANOVA), using SPSS for Windows (version 20.0). A p-value of <0.05 was considered statistically significant.

The sound recordings of the laser experiments were compared to the sound production of a Osseostap microburr, 8 mm diamond drill (Bien-Air, Bienne, Switzerland). In these experiments the stapes was directly placed on the polyacrylamide gel and fixed between three pin needles. Without fixation, the stapes footplate tends to spin with the rotating drill. As the drill needs time to speed up, timeframe of measurement was prolonged to 1 second. Other test settings were the same for all of the experiments.

Laser

A 980 nm hand-held, battery-driven Diode laser, with a 200 µm fiber (FOX, A.R.C. Laser

Nurnberg, Germany) was used. A single-pulse laser beam of 3.0 Watt was fired for 100 ms in all of the experiments. The total energy over the irradiated surface (fluence) was 955 J/cm^2. Using lower settings will not lead to footplate perforation. These settings correspond with settings currently used in daily ENT practice. Before starting the experiments, the laser tip was carbonized by using the laser on a wooden spatula, at 3W, 100 ms, 5 pulses.

Results

Mechanical effects

The 980 nm Diode laser wavelength is strongly absorbed in pigmented areas. The white footplate of the stapes is not a pigmented area. We therefore carbonized the fiber tip prior to firing the laser (see **Figure 2a** and SDC1, supplemental digital content available n the online article) to optimize bone ablation. After carbonization of the fiber at a different, pigmented location, the fiber was ready for use. This process also needs to be carried out when using the KTP laser. However, when using the KTP laser, carbonization is achieved at a much faster rate. During the pulse, a large area of the stapes footplate was carbonized. A smoke plume formed at the site of the perforation, which is evidently visible in the videos online. A small conical perforation and a large rim of carbonization were seen following the laser pulse (see **Figure 2b** and SDC2).

When looking into the artificial vestibule from the side, only minimal effects were witnessed during the laser pulse. The fiber tip lightened up, due to extensive heating. No effects in the vestibule were seen. (**Figure 2c** and SDC3). When using the laser through an already existing perforation, a small flow of the NaCl solution could be seen through the vestibule (see the red arrow in **Figure 2d**). The movements were better seen on the high speed imaging video online (Video; SDC 4).

Thermal effects

When using the Diode laser directly on a slab of gel, we could see heat clearly penetrating the gel (see the blue arrow in **Figure 3a** and SDC5). A very narrow cone of heat penetrated the gel. Using the Schlieren Technique, two strips appeared on the video, representing the borders of the cone. When looking at the vestibule from the side, only minimal heating of the vestibule was seen during perforation of the stapes footplate, just below the footplate (red arrow, **Figure 3b**, and SDC6). When a second laser pulse was applied to the same spot, firing into vestibule, the typical penetrating heating pattern was seen again (see blue arrow in **Figure 3c** and SDC7).

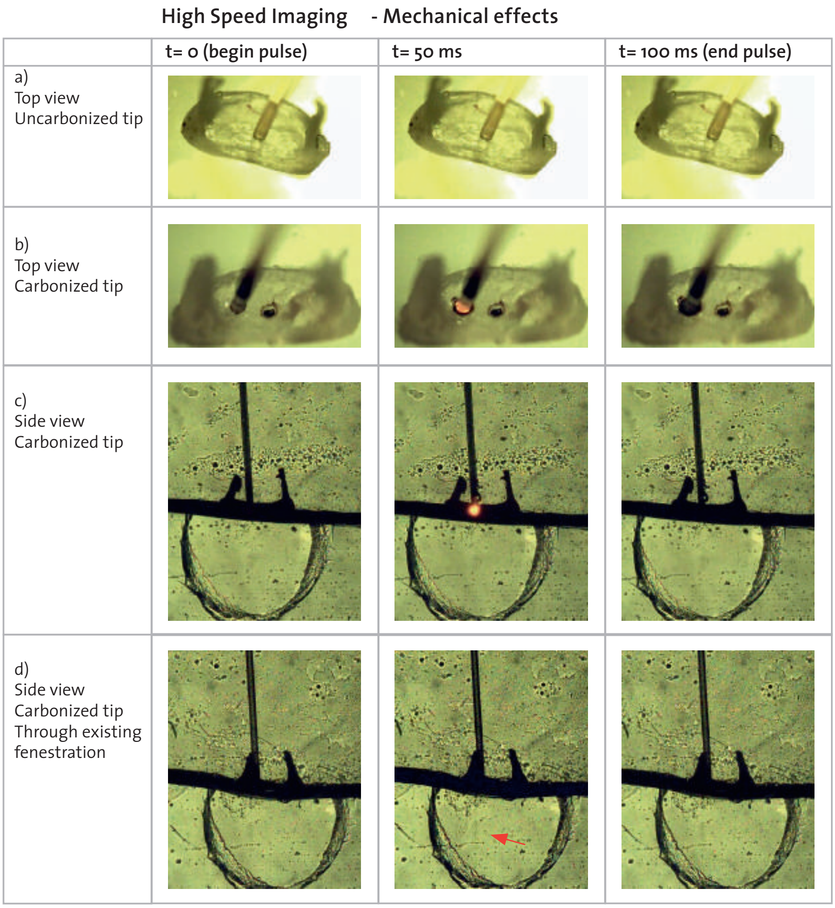

Figure 2 Mechanical effects

High speed Imaging. Snapshots at t=0, 50 ms, and 100 ms, during single shot laser fenestration. Pulse 100 ms at 3W

a) Top view, no carbonization of tip, no effects on footplate. (see also SDC 1)

b) Top view, carbonization of tip. Small fenestration with thick carbonized rim (see also SDC 2)

c) Side view, carbonized tip. Heating of tip. No mechanical effects (see also SDC 3)

d) Side view, carbonized tip, through existing fenestration. In the vestibule a flow occurs (red arrow). (see also SDC 4)

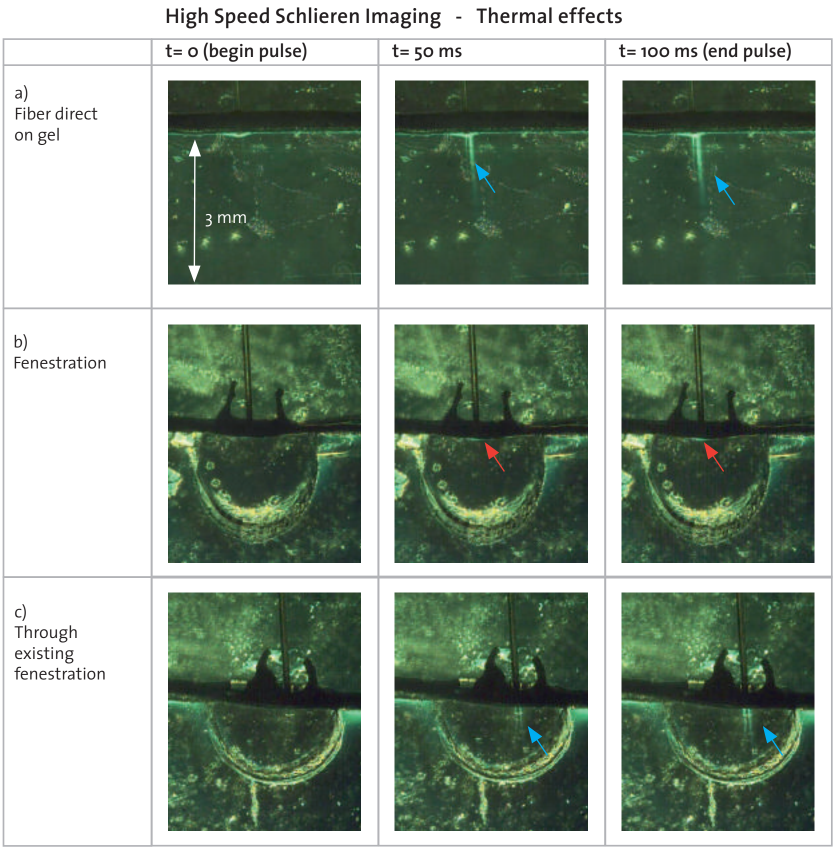

Figure 3 Thermal effects, High Speed Schlieren

Snapshots at t=0, 50 ms, and 100 ms, during single shot laser fenestration. Pulse 100 ms at 3W

a) Fiber direct at gel. Note the penetration depth, blue arrow. (see also SDC 5)

b) Side view of fenestration, with carbonized tip. Note only superficial heating, red arrow. (see also SDC 6)

c) Side view when laser hits existing perforation. Note the penetration depth, blue arrow (see SDC 7)

Acoustic effects

The Diode laser generated limited noise. Fourier analyses showed that the Diode laser generated mostly low-frequency sounds, around 100-150 Hz. The total loudness of the noise produced during the 100 ms laser pulse was 61 (SD 7.2) dB SPL. The highest impulse noise within this signal, consisted of 52 (SD 7.8) dB(A), at 150 Hz (**Figure 4**). This is comparable to the noise produced by the KTP laser and lower than that produced by the CO_2 and Thulium laser (**Figure 5**)[13]. Although the produced sound seems to be rather loud, the traditionally used microburr produces even louder noises. For example, the Osseostap diamond drill (BienAir, Noirmant, Switzerland) generates an impulse noise of 95 (SD 6.9) dB(A) at 2700 Hz.[13] As our hearing is more susceptible for sound at this higher frequency, the potential harmful effects are considered much larger than of low frequency noise. Using high speed imaging, flows were seen in the vestibule during laser pulse through an existing perforation only. These movements could have been pressure waves, which are potentially damaging to the saccule. If these pressure waves would have been substantial and thus potentially damaging, they would have resulted in deviations in the raw audio data. We did not identify abnormal results in the audio clips that could have represented pressure waves.

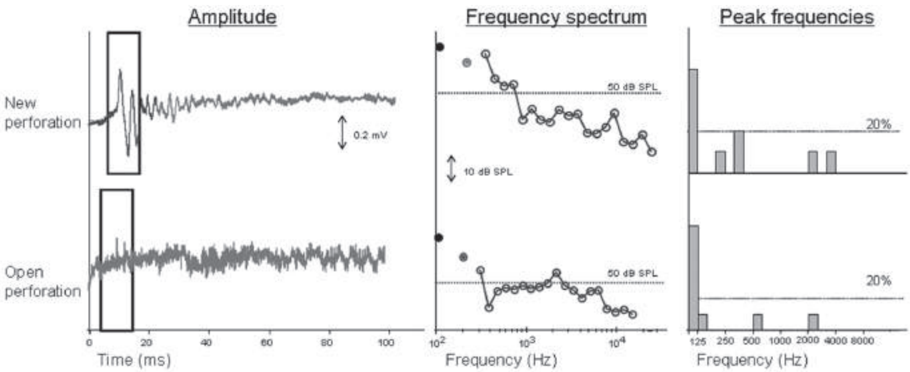

Figure 4 Acoustic measurements
Two raw audio recordings are shown; one when making a new perforation (top), one when firing through an existing perforation (bottom). Over the time frame of 10 ms with largest amplitudes (box), a frequency spectrum was obtained. This frequency spectrum is shown with a reference line of 50 dB SPL in the central column. Of each spectrum the peak frequency was located (black dot). In the right panel the peak frequencies were shown for all the measurements taken

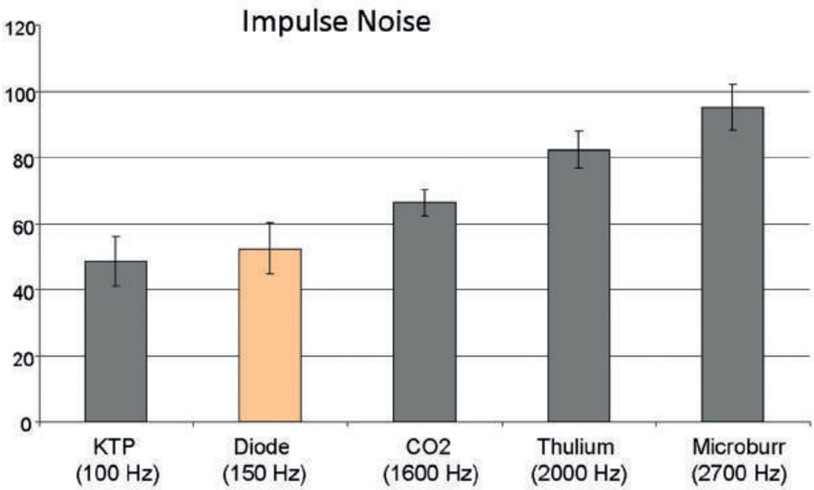

Figure 5 Comparison of the impulse noise generated by the Diode Laser, compared to other lasers and drill. The peak frequency of the noise is shown between brackets

Discussion

In this study, special imaging techniques were applied to visualize mechanical and thermal effects during stapedotomy using the Diode (980 nm) laser in an inner ear model. It is assumed that damage to the inner ear occurs as a result of heating of the inner ear fluids. Especially larger increases in temperature or prolonged exposure, have been associated with vertigo, tinnitus and hearing loss.[14,15] Furthermore, mechanical trauma has been suggested to cause perceptive hearing loss as a result of the formation of sound pressure waves. The mechanical and thermal effects caused by the Diode laser were minimal.

We used the Schlieren imaging to measure relative changes in heating, at high speed. This technique provides a good insight in the thermodynamic processes inside the inner ear, which give a good prediction of potential damage to inner ear function. When comparing the results of the Diode lasers to the lasers that have previously been evaluated by our research group, the same amount of heating was seen in the experiments with the Diode laser as was seen in the KTP laser, around 4 degrees Celsius [12]. Most researchers use thermocouples to measure heat.[16-18] Outcome measurements differ greatly when using thermocouples. The thermocouples only measures heat at one distinct point and the results are highly dependent on the placement of the thermocouples in relation with the stapes footplate. Also size and material of the thermocouples affect the outcome. During fenestration, the thermocouples can show artifacts due to direct illumination of the laser light. These limitations make thermocouples not ideal for measuring heat, especially when the area of heating is small and exposure time is limited. For the Argon laser, temperature increases between 0.4°C[16] and 25°C[19] have been found using different set-ups. When choosing which laser to use in stapedotomy, a comparative measurement of heating patterns would provide sufficient information.

It is important to note that carbonization of the fiber tip is a requirement for bone ablation. Carbonization of the tip is achieved by firing the laser on a wooden spatula or by using the laser in a vascular area, for instance superficial muscle. A tip that is not carbonized will not affect the stapes footplate in any way, not even when fluencies are doubled. The main drawback of prior carbonization is that it is not possible to standardize the process of carbonization. The degree of carbonization differs depending on the material used for carbonization and exact distance to the object used for carbonization, laser settings, etcetera. The degree of carbonization determines the potency of the laser pulse. The surgeon should have a clear understanding of this mechanism. When the laser pulses seem to have limited ablative effects, this can be resolved by increasing the degree of carbonization of the tip of the laser fiber. This is a helpful technique in avoiding the urge and need for increasing the laser settings. In the future, the use of a commercially blackened tip of the fiber, might overcome these problems. Such a blackened tip has been tested in Neurosurgical cases and found successful.[20]

The carbonization of bone requires temperatures of 200 to 300°C. While the bone is ablated, some of the heat is transferred to the vestibule. When the same spot is hit twice, the 980 nm wavelength penetrates the vestibule. However, absorption of the 980 nm wavelength in the perilymph is limited. Nonetheless, as with all lasers that are characterized by limited absorption in watery solutions, the Diode laser could theoretically damage the well-pigmented cells of the neuro-epithelium. For safety reasons, it seems advisable for the surgeon to avoid shooting on the same spot twice while making the rosette figure on the footplate. We are currently working on a model to investigate this effect in relation to sensorineural hearing loss (SNHL) and to estimate the actual risks.

Only when firing the laser through an existing perforation, a flow occurs in the vestibule. We did not find matching pressure waves in the audio data. These movements have not been described earlier. To understand the possible effects of these movements, special visualizing techniques are needed to visualize them more clearly.

The extent of possible damage due to intra-operative noise production depends on the pulse duration, number of pulses and the frequency and loudness of the sound produced

by the laser.[21,22] There appears to be a large diversity in individual sensitivity in humans to these impulse noises.[21] As a result, there is no general cut-off point that determines when the produced sound is loud enough to result in damage.
The 2940 nm Er-YAG laser is known for its explosive bone ablation, causing impulse noises of 140 to 160 dB(A).[3] In clinical series, some expert surgeons report a decline in bone conduction at 4 kHz up to 8%, while others find no change in bone conduction.[19,23-26]
The sound production of the 980 nm Diode laser is low in all frequencies and therefore neglectable as a source of SNHL.
Overall, in our setup the 980 nm Diode laser, generates only minimal side-effects, and from that standpoint can be safely used in clinical settings. Clinical studies need to be undertaken to verify benefits for both patient and surgeons.

Conclusion

The Diode (980 nm) laser is a useful tool in performing laser-assisted stapedotomy. Mechanical, thermal and acoustic effects are minimal and well within safety limits.
Due to Diode laser high energy-efficient properties it can be battery-operated, which is an advantage when there is limited space in the overcrowded operating theater. Due to the relatively low operational cost this Diode laser may become a cost effective device even in low-volume stapes surgery clinics.

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7

Effect of KTP Laser Cochleostomy on Morphology in the Guinea Pig Inner Ear

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ORL J Otorhinolaryngol Relat Spec 2014;76:70-75

Abstract

Background: The main advantage of using the KTP (Potassium-Titanyl-Phosphate) laser for stapedotomy, instead of the conventional micropick instrument, is less chance of mechanical damage. However, the KTP laser could theoretically inflict damage to inner ear structures.

Hypothesis: KTP laser light (λ = 532 nm) is hardly absorbed in perilymph, but is absorbed in solid structures. The aim of this pilot study was to assess if damage occurred after KTP laser cochleostomy in an animal model and, if so, to what extent and at which settings.

Materials and Methods: In six guinea pigs a KTP laser cochleostomy at the basal turn was created. Laser settings of 1, 3 and 5 Watt and 100 ms pulse time (n = 2 each) were used. Histological preparations were studied for damage to neuro-epithelial cells and intrascalar blood.

Results: No damage to inner ear neuro-epithelial cells was observed, even at the highest power. Blood clots in the scala tympani from vessels in the cochlear wall were seen. Effects were minimal in lowest, currently clinically used, settings.

Conclusion: KTP laser cochleostomy gives no damage to inner ear neuro-epithelial cells, but may cause intrascalar hemorrhages.

Introduction

Traditionally, in otosclerosis surgery, a fenestration in the footplate is made by a micropick instrument or a microburr. These contact methods entail risks, e.g. bleeding, acoustic trauma to the inner ear or fracture of the stapes footplate.[1] To minimize these risks, a laser can be used for fenestration. Different lasers are available, e.g. Argon (wavelength (λ) = 480, 514 nm) laser, KTP (Potassium-Titanyl-Phosphate, λ = 532 nm) laser, Erbium-YAG (Erbium-yttrium-aluminum-garnet, λ = 2940 nm) laser and CO_2 (λ = 10600 nm) laser. In practice, the choice depends mainly on surgeons' preference and availability.

Side effects, when using a laser, consist mainly of heating of inner ear structures. If the laser energy is mainly absorbed in water, which is the case for the CO_2 laser, heating of the perilymph may occur. The KTP and Argon lasers seem preferable for laser-assisted stapedotomy, as their wavelength is hardly absorbed in water, minimizing the risk of heating.[1-3] However, theoretically, when using a KTP laser, there is risk of direct damage to neuro-epithelial cells. The transmission of the laser light through the perilymph may result in absorption of residual energy in the neuro-epithelium in the vestibule. Authors have suggested that this could explain the (temporary) vertigo complaints in patients after KTP laser assisted stapedotomy.[1,4-6]

The aim of this study is to determine whether in vivo application of KTP laser light causes inner ear damage in an animal model, as assessed in histological preparations and, if so, to what extent and at what power settings.

Material and Methods

Animals

Six albino female guinea pigs (weight: 350-500 gram; strain: Dunkin Hartley; supplier: *Harlan Laboratories, Horst, The Netherlands*) were used. The study protocol was approved by the Animal Ethical Committee of the University Medical Center Utrecht under number 2011.I.09.091.

A guinea pig model was used, since the thickness of the bone of the basal turn of the guinea pig cochlea is comparable to the thickness of a human stapes footplate (150-200 μm). Furthermore, the cross-sectional diameter of the guinea pig cochlear basal turn corresponds to the depth of a human vestibule. Finally, the guinea pig cochlea is easily accessible in surgery.[7,8]

Anesthesia

Anesthesia was initiated with 0.5 ml/kg Hypnorm® (0.315 mg/ml fentanyl + 10 mg/ml fluanisone) administered intramuscularly. Further anesthesia was induced with a gas mixture of N_2O (2 L/min), O_2 (1 L/min) and 2% isoflurane using a mouth cap. To prevent bradycardia following anesthesia, 0.1 ml/kg atropine was administered intramuscularly. The animal was subsequently tracheostomized and artificially ventilated with a gas mixture of N_2O and O_2 (2:1) and 1-1.5% isoflurane (±35 cycles/min respiration rate, 2-2.3 kPa) throughout the experiment. Heart rate was monitored and body temperature was maintained with a heating pad. After surgery, the animals were kept under general anesthesia for four hours, in order to be able to see late effects of inner ear damage (e.g., oedema) in the histological preparations.

Surgery

After local analgesia with Xylocaïne® (1% lidocaïne, 2% epinephrine), a retroauricular incision was made to expose the right bulla. The bulla was opened and a clear overview of the middle ear was created. The basal turn of the cochlea was identified.

A 532-nm KTP laser (*IDAS, Quantel Derma, Erlangen, Germany*) coupled to a fiber hand piece (*Endo-ENT, Biolitec, East Longmeadow, Massachusetts, USA.* Diameter: 200 micron) was used to make the fenestration. For a stapedotomy, a setting of 1 Watt for 100 ms is used clinically. The power of laser pulses used in these experiments was 1 Watt, 3 Watt or 5 Watt for 100 ms (for corresponding fluencies, see **Table 1**). One Watt corresponds to current clinically used power[9-11]. At the basal turn of the cochlea a rosette of four fenestrations was created (see **Figure 1**). Left (untreated) cochleas functioned as controls. Four hours after fenestration the animals were euthanized with an intracardial injection of 0.5 ml Nembutal® (pentobarbital).

Histology

The cochleas were fixed by intracardial perfusion with a fixative consisting of 3% glutaraldehyde, 2% formaldehyde, 1% acrolein and 2.5% DMSO in 0.08 M sodium cacodylate buffer (pH 7.4) followed by immersion in the same fixative for minimally 3 hours at 4 °C. Further processing of the cochleas was performed according to a standard protocol.[12]

For histology, fixated cochleas were cut at 1-μm slices. Every 20th section was collected for staining with methylene blue and azur II in sodium tetraborate and used for light microscopic evaluation and quantitative analyses.

Table 1

Power (W)	Pulse time (ms)	Spot diameter (μm)	Fluency (J/cm²)
1	100	200	318
3	100	200	955
5	100	200	1592

KTP laser settings

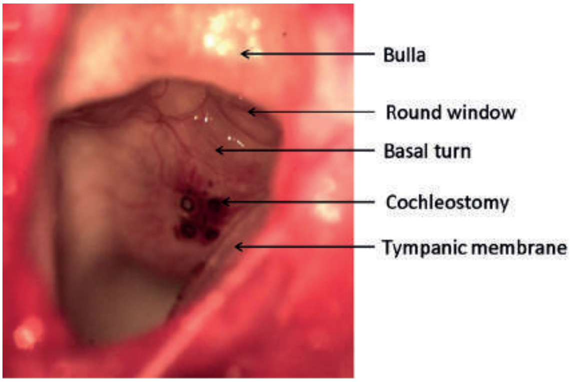

Figure 1 Intraoperative view of laser area
The right bulla was opened and the basal turn of the cochlea is visible. A rosette of laser fenestrations was created, in this example at a power of 3 Watt. At the rim of each laser fenestration, carbonization can be seen

Analysis of histology

All preparations were reviewed by two observers (DK, JP). In case of discussion a third observer was consulted and consensus reached. Each preparation was reviewed for damage to the organ of Corti, to vascular structures (stria vascularis) and to the cochlear wall. Photographs were taken using a microscope-mounted camera (*Leica DC300F, Leica Microsystems GmbH, Wetzlar, Germany*).

Results

In this experiment, three groups (1, 3 and 5Watt; *n* = 2 each) were used to determine whether in vivo application of KTP laser light causes inner ear damage and, if so, to what extent and at what power.

As expected, bone ablation was more extensive at higher laser power, i.e. fenestrations that were created with 1 W were smaller than the fenestrations created with 5 Watt. Representative preparations of a cochlea, fenestrated at different laser settings, are shown in **Figure 2**. At a power of 1 W, the laser was hardly able to fenestrate the wall of the basal turn of the cochlea (**Figure 2a** and **2b**). At a power of 3 W fenestration was possible (**Figure 2c** and **2d**). Finally, in the 5 W mode large parts of the cochlear wall were ablated and substantial smoke arose (**Figure 2e** and **2f**).

In none of the cochleas light-microscopical signs of damage to the organ of Corti were visible. The stria vascularis was intact in all cases. No thermal signs were seen opposite to the irradiation holes, not even at the highest settings.

All treated cochleas, however, showed blood in the scala tympani of the basal turn. This intrascalar blood extravasated from vessels in the cochlear wall close to the area where the laser fenestrated the bone of the basal turn, as can be seen in **Figure 2b** and **2d** and, in detail, in **Figure 3**.

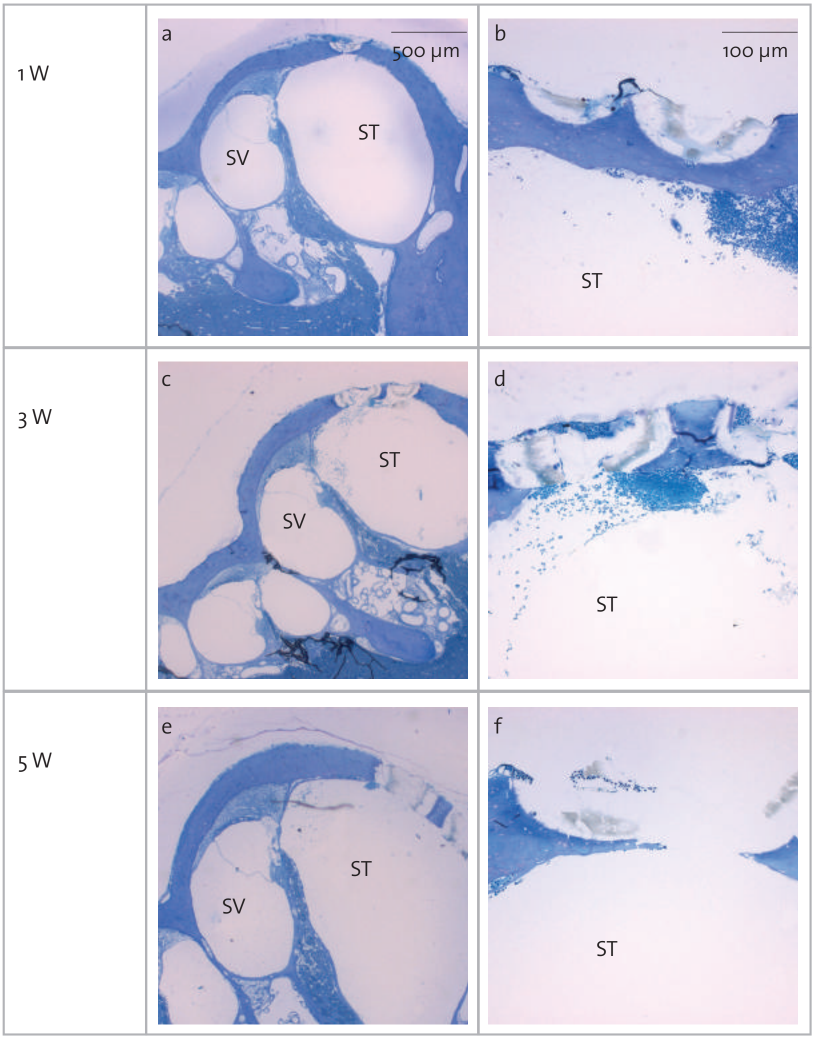

Figure 2
Detail images of cochleostomies at different power settings (W= Watt; ST= scala tympani; SV=scala vestibuli)

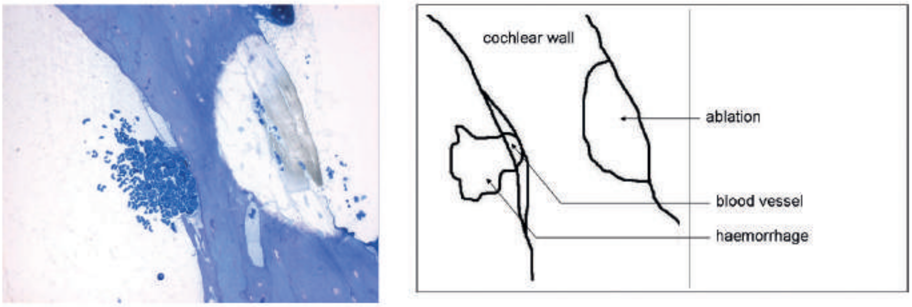

Figure 3 Detail of laser fenestration

Discussion

The aim of this study was to show whether damage to inner ear tissue occurred during laser-assisted cochleostomy. We expected to see damage to the organ of Corti in histological preparations, when applying substantial power. This damage was not observed, not even at settings five times higher than clinically used. In addition, no thermal effects were seen opposite to the irradiation site.

A possible explanation for the absence of neuro-epithelial damage is that the energy of the laser light is absorbed in the haemoglobin molecules of the blood vessels in the cochlear wall and therefore the laser does not inflict damage at deeper structures.[13] Also, the excessive energy might be absorbed in the bone of the cochlear wall generating heat.[14]

We did find intrascalar blood in all treated animals. There was no correlation between laser power and blood clot size. Large variances in volumes of blood clots were observed. This is probably due to factors that have no relation with laser power, such as vascular anatomy.

It is not clear whether these intrascalar blood clots also occur when using a different laser. After CO_2 laser cochleostomy in guinea pigs, no damage to the organ of Corti or intrascalar blood was observed.[15] A CO_2 laser fenestration in cats, however, showed reactive hemorrhage in the saccular wall.[16,17]

The clinical relevance of blood in the inner ear remains unclear. Autologous blood of guinea pigs (3 μL) in the scala tympani showed that hearing thresholds deteriorated in the high frequency range.[18] Part of the threshold shift was permanent and therefore it was concluded that intrascalar blood may cause harmful effects to the cochlea. In stapedotomy the blood is located in the vestibule, possibly causing vertigo. Several authors report (transient) vertigo following KTP or Argon laser stapedotomy in patients, ranging from 6.6 to 39%.[1,4-6] As blood in the vestibule could be absorbed in time, clinical symptoms of vertigo subside. Especially, regarding the minimal blood clots seen in the 1W group, this seems plausible. Further research on histology, in combination with functional outcome, could help us to better understand the clinical meaning of these blood clots.

Conclusion

The application of a KTP laser assisted cochleostomy causes no damage to tissues in the cochlea. Intrascalar blood clots were observed extravasating from vessels in the cochlear wall, which might be related to vertiginous spells in patients after laser assisted stapedotomy.

Acknowledgements

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8

Influence of Laser-assisted Cochleostomy on acoustically evoked Compound Action Potentials in the Guinea Pig

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Abstract

Hypothesis: Making a cochleostomy with a laser can affects inner ear function.
Background: Different types of lasers can be used to create a fenestration in the footplate of the stapes during stapedotomy. Due to variations in absorption spectra of the laser light in various tissues or fluids, each laser has its own characteristics and possible side effects.
Materials and Methods: The basal turns of the cochleae of twenty guinea pigs were fenestrated using four types of lasers (KTP, Diode, CO_2, Thulium; all groups n = 4). A control group (n = 4) was included to correct for effects of the surgery alone. At three different time points acoustically evoked compound action potentials (CAPs) were recorded at five frequencies and at different sound pressure levels. N_1-P_2 amplitudes were measured and subsequently thresholds were calculated. A repeated measures analysis of variance was used to investigate differences between groups.
Results: There was a decrease in CAP amplitudes and an increase in CAP thresholds after cochleostomy with each laser. The increase in thresholds was significantly larger for higher frequencies. The Thulium laser evoked the largest threshold shifts, the KTP laser the smallest with the CO_2 and Diode lasers in intermediate positions. Overall, there was an increase in latencies after treatment.
Conclusion: Laser treatment on or near the cochlea can cause damage to the sensitivity of the cochlea for sound. The Thulium laser seems to be the worst choice in this respect.

Introduction

Using a laser for fenestration of the footplate in stapes surgery can reduce the complication rate due to conventional contact methods of perforation.[1] With a micropick instrument or microburr, substantial mechanical energy and sounds are generated, which can damage inner ear structures. The use of a non-contact method does not entail this risk. Until now, various laser types have been proposed to be safe for use in stapedotomy. However, each of these lasers has its own specific characteristics which influence its potential risk of damaging the inner ear structures. The wavelength of the laser light will determine the level of absorption in different tissues and media, for instance in bone, perilymph or basilar membrane and therefore will determine the associated side effects and their size. The traditionally used lasers, such as the Argon (wavelength (λ) = 488 / 514 nm) and potassium titanyl phosphate (KTP; λ = 532 nm) lasers, bear the risk of damaging the inner ear directly.[2,3] Due to their light transmission through watery liquids, such as the perilymph, unwanted energy is absorbed in the area of the neuro-endothelium of the vestibule. It has been suggested that this could explain the (temporary) vertigo complaints in patients after KTP laser assisted stapedotomy.[2-4]

The CO_2 laser (λ = 10.6 µm), used in both continuous wave and pulsed wave mode, is well absorbed in both fluid and bone, implying a controlled perforation. Excess energy is highly absorbed by the perilymph and therefore will not reach the neuro-epithelium.[5,6] However, this fast absorption can cause local heat formation, potentially causing vertigo, tinnitus and hearing loss.[7]

Recent developments include the introduction of the continuous wave 2 µm laser (usually referred to as Thulium laser) and the 980 nm Diode laser. The Thulium laser has the advantage of a relatively high absorption in water. Excessive energy, however, will be able to penetrate the vestibule much deeper than with a CO_2 laser.[5]

The 980 nm Diode laser is interesting to use in current economical times. The devices are small, battery driven and relatively inexpensive. The 980 nm wavelength has certain surgical advantages, its high absorption in hemoglobin, makes it an excellent candidate to treat vascularized lesions.[8,9] Its effects in stapedotomy are more difficult to predict. The energy at this wavelength is partially absorbed in the perilymph, but most of it will be transmitted through the perilymph. It could theoretically cause both heating near and direct damage to inner ear cells.

Previous research in artificial models on heating, mechanical and acoustic effects showed remarkable differences between the different lasers mentioned above.[5,10] The question remains whether these effects actually affect inner ear function, or whether they are clinically irrelevant. We chose a guinea pig model to investigate in vivo effects, because the basal turn of the cochlea in this species is easily accessible and the thickness of the cochlear wall of approximately 120-160 µm, is comparable to the 150-200 µm of a slightly thickened otosclerotic footplate.[11-13] Further, the cochlear function can be measured by recording acoustically evoked Compound Action Potentials (CAPs).

The aim of this study is to compare the effects of different laser types (KTP, Diode, CO_2 and Thulium), on inner ear functionality in the guinea pig. The results will help in establishing the optimal laser choice for stapedotomy procedures.

Material and Methods

Animals

Twenty albino guinea pigs (weight: 350-550 gram; strain: Dunkin Hartley; supplier: Harlan Laboratories, Horst, The Netherlands) were used. The study protocol was approved by the Animal Ethical Committee of the University Medical Center Utrecht (under number DEC2012.I.12.126).

All 4 laser groups consisted of four animals. A fifth group (n=4) was designated as a control group. Animals in this group underwent the same procedures, but no laser fenestration occurred. The group was added to control for influences caused by the surgical procedures or anaesthesia.

Anaesthesia was initiated with 0.5 ml/kg Hypnorm® (0.315 mg/ml fentanyl + 10 mg/ml fluanisone) administered intramuscularly. Further anaesthesia was induced with a gas mixture of N_2O (2 L/min), O_2 (1 L/min) and 2% isoflurane using a mouth cap. To prevent bradycardia following anaesthesia, 0.1 ml/kg atropine was administered intramuscularly. The animal was subsequently tracheostomized and artificially ventilated with a gas mixture of N_2O and O_2 (2:1) and 1-1.5% isoflurane (±35 cycles/min respiration rate at maximum 2-2.3 kPa) throughout the experiment. Heart rate was monitored and body temperature was maintained with a heating pad. After surgery, the animals were kept under general anaesthesia for 4 hours, in order to be able to detect late effects.

Surgery

After local analgesia with Xylocaïne® (1% lidocaïne, 2% epinephrine), a retroauricular incision was made to expose the right bulla. The bulla was opened and a clear overview of the middle ear was created. The basal turn of the cochlea was identified. Fenestrations were made by one of the lasers. In total a rosette of 4 fenestrations was made (see **Figure 1**). In the control group animals underwent the same surgical procedures, but no fenestration in the cochlea was made.

To measure the functionality of the guinea pig cochlea, CAPs were recorded. A golden ball electrode was positioned in the round window niche (just superior to the round window membrane). A reference electrode was positioned rostrally of the brain in the skin on the forehead and finally a ground electrode was placed in the right hind leg. The pinna of the right ear was repositioned to assure normal access of sound to the outer ear canal. Four hours after fenestration the animals were euthanized with an intracardial injection of 0.5 ml Nembutal® (pentobarbital).

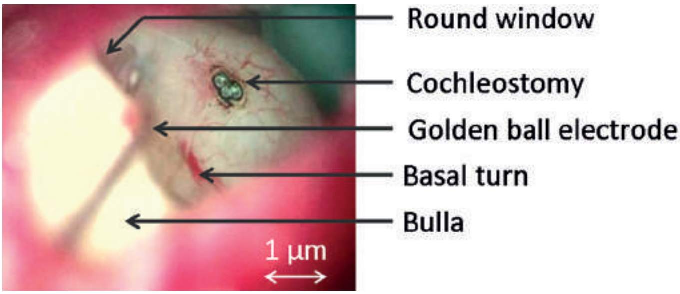

Figure 1 Intraoperatiev view
The bulla was opened. A rosette cochleostomy is created in the basal turn (in this example by the CO_2 laser). The golden ball electrode is placed in the round window niche.

Stimulus Generation and Electrophysiological methods

To record acoustically evoked CAPs, the following procedures were performed: Stimuli were generated by a pc with custom-designed software in a Delphi 7® (Borland) programming environment, and were fed to a 24-bit DA converter (RP2.1, Tucker-Davis Technologies (TDT, Florida, USA) at a sampling rate of 49 kHz. Acoustic stimuli for CAP measurements were presented as 12 ms (0.5 kHz) or 8 ms (1-16 kHz) tone bursts, with cos^2-shaped rise and fall times of 4 ms at 0.5 kHz, 2 ms at 1 kHz, 1.5 ms at 2 kHz and 1 ms at 4, 8 and 16 kHz. The acoustic signal was fed via a pair of attenuators (PA5, TDT) and a headphone amplifier (HB7, TDT) to a speaker (Blaupunkt, Berlin, Germany, PCxb352, 4 Ohm, 30 W) approximately 5-10 centimetres from the right ear of the animal. Sound levels were determined with a sound level meter (2610, Brüel & Kjær, Nærum, Denmark) and a 1/4" condenser microphone (4136, B&K, Nærum, Denmark), calibrated with a 94 dB SPL 1 kHz reference source. Tonebursts were presented in trains with an interstimulus interval of 99 ms. Consecutive tonebursts were of opposite phase (condensation first or rarefaction first). Cochlear potentials were differentially amplified (5,000x or 10,000x), band-pass (1 Hz - 30 kHz) filtered (preamplifier 5113, EG&G Instruments, Princeton, USA) and AD converted at 49 kHz (RP2.1, TDT). Responses to stimuli with opposite phases were separately averaged (to a maximum of 250 sweeps/polarity) and stored for off-line analysis. The sum of the responses to the two opposite phase acoustic stimuli yielded the CAP waveforms.

CAPs were measured at three different times: 1) "prelaser", just before laser fenestration; 2) "directly postlaser", directly after laser fenestration; and 3) "late postlaser", four hours after laser fenestration. During the experiment, the bulla was kept clean from blood. Per frequency, we started with a high level of stimulation. In subsequent steps of 10 dB attenuation, CAPs were recorded until reaching the noise threshold value of approximately 3 µV.

Using MATLAB software (version 7.11.0; Mathworks, Natick, MA, USA) the amplitudes of the CAP between the first negative peak (N1) and the subsequent positive peak (P2) were measured (Figure 2). Threshold levels were defined as an isoresponse level at 3 µV.

Lasers

Four different lasers were investigated: KTP, Diode, CO_2 and Thulium laser. The 532 nm KTP laser (IDAS, Quantel Derma, Erlangen, Germany) was coupled to a fiber hand piece (Endo-ENT, Biolitec, East Longmeadow, Massachusetts, USA, spot size 200 micron). A 980 nm Diode laser (Atos Medical BV, Zoetermeer, The Netherlands) was used with a 200 micron fiber. The 2 µm continuous wave Thulium laser (RevoLix Jr. Thulium laser system, Lisa Laser Products, Katlenburg-Lindau, Germany) was used with a 273 micron silica fiber. An articulated arm and micromanipulator was used for the CO_2 experiments (λ = 10.6 µm, Ultrapulse Encore CO_2 laser, Lumenis Ltd., Yokneam, Israel, spot size 250 micron).

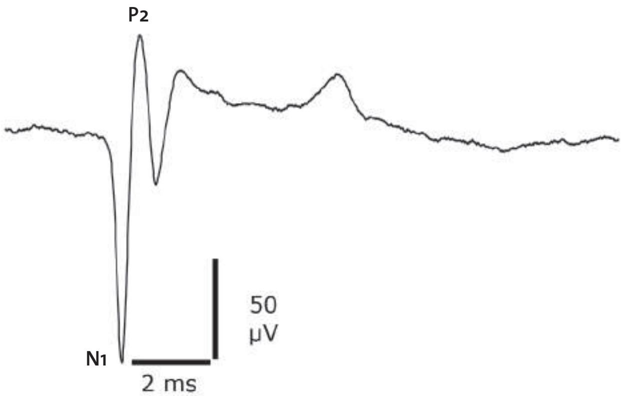

Figure 2 Compound action potential
Example of compound action potential (16 kHz, 93 dB SPL). Amplitude is measured in microvolts between first negative peak (N1) and subsequent positive peak (P2)

All lasers were used in a single pulse mode, where the pulse lasted 100 ms. KTP, Diode and Thulium fiber laser tips were carbonized before starting the experiment, by firing 5 laser pulses on a wooden spatula. This increases speed of the ablation mechanism and is standard surgical procedure.[14] The laser settings were the lowest settings needed to ensure bone ablation, known from current clinical practice [15-19]. The fluencies (in J/cm^2) are higher when a laser wavelength has less bone ablating capacity; more energy is needed per surface to insure bone ablation. The laser settings and fluencies are displayed in **Table 1**.

Four hours after fenestration the animals were euthanized with an intracardial injection of 0.5 ml Nembutal® (pentobarbital).

Table 1 Laser specifications

Group	Wavelength	Power	Time	Spot diameter	Fluency
Control	-	-	-	-	-
KTP	532 nm	1 W	100 ms	200 μm	318 J/cm^2
Diode	980 nm	2.5 W	100 ms	200 μm	796 J/cm^2
CO_2	10.6 μm	2 W	100 ms	250 μm	407 J/cm^2
Thulium	2 μm	5 W	100 ms	273 μm	857 J/cm^2

Laser specifications are shown of each laser, wavelength and laser settings. Laser settings consist of power per laser pulse (in Watt), time of laserpulse (in ms) en laser spot diameter (in μm). The total energy used per surface (fluency, J/cm^2) is shown in the most right column

Statistical analysis

We used SPSS for Windows (version 20) for the statistical analyses. We used a repeated measures analysis of variance (ANOVA) to compare differences in thresholds between the control and laser groups, with time (prelaser, directly postlaser and late postlaser) and frequency as within factors. When the assumption of sphericity was violated, the Greenhouse Geisser correction was applied.

We also performed a post-hoc Bonferroni and Dunnett analysis, to compare laser groups directly with the control group.

Results

Figure 3 shows input-output curves for all 5 groups at 16 kHz stimulation. At this frequency, the effects were largest. In the control group amplitudes deteriorated slightly over time. However, much larger deteriorations of CAP amplitudes over time were found in all laser treated groups, with the Thulium laser at the most extreme end of the damage spectrum.

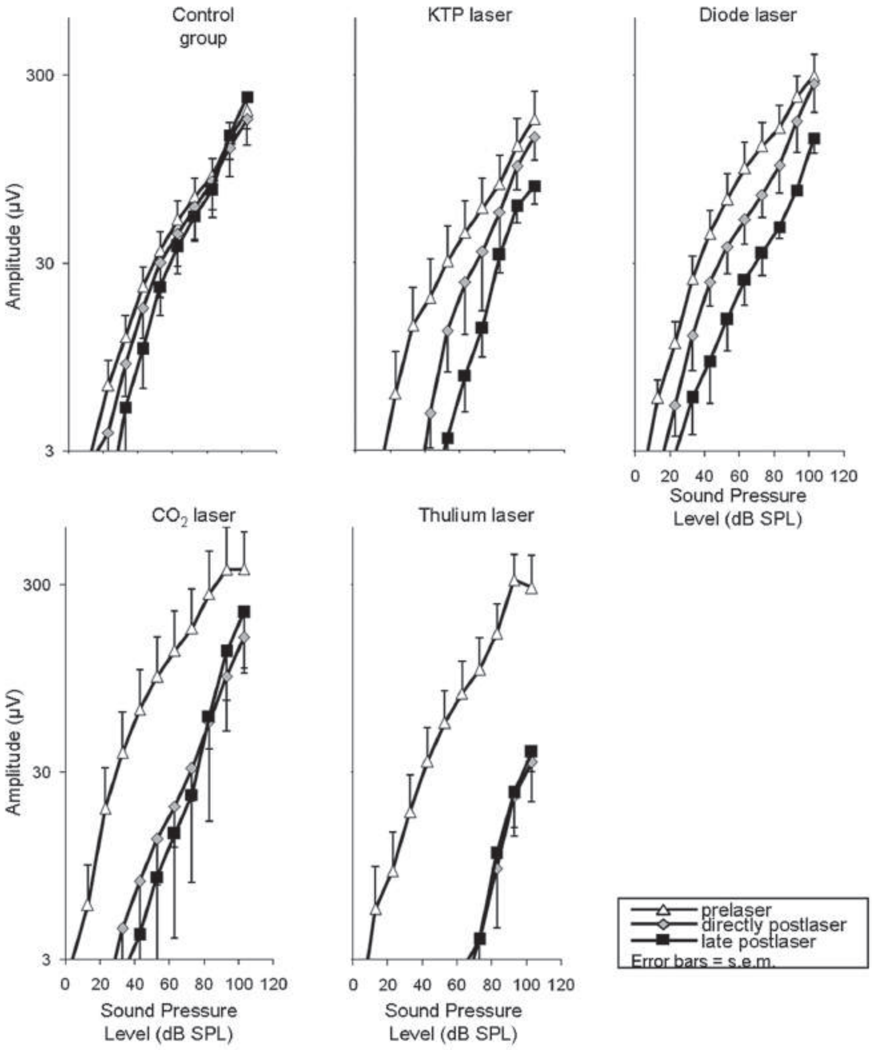

Figure 3 CAP amplitudes
CAP amplitudes are shown for all laser groups and the control group. For each groups, measurements are shown before creating the cochleostomy (“prelaser”), directly after (“directly postlaser”) and 4 hours later (“late postlaser”). Error bars represent standard error of means (s.e.m.). Amplitudes were measured at different stimulation levels (in dB SPL), until they reached the 3 µV threshold

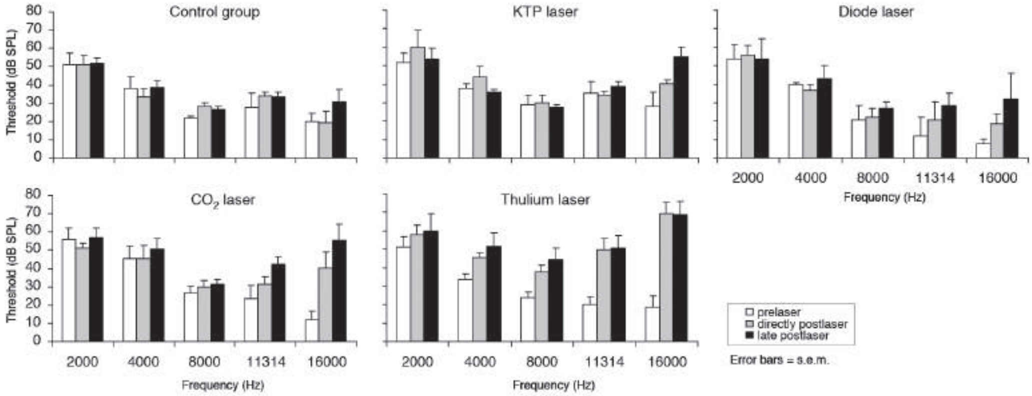

Figure 4 Thresholds
For each control and laser groups thresholds (CAP isoresponse levels at 3 μV) are presented for the different frequencies. For each frequency,thresholds are shown before creating the cochleostomy ("prelaser"), directly after ("directly postlaser") and 4 hours later ("late postlaser"). Error bars represent standard error of means (s.e.m.)

CAPs were characterized and further analyzed on the basis of isoresponse levels of 3 μV, which is the point at which the input output curves cross the horizontal axis in **Figure 3**. These thresholds are depicted as a function of frequency and time in **Figure 4**. In the control group, thresholds remained stable throughout the experiment. The minimal changes in the higher frequencies were not statistically significant. Also, rmANOVA on possible differences between the thresholds before the use of the laser for all groups, did not show a significant difference ($F = 0.9$, $df = 4$, $p > 0.05$) for all frequencies.

chapter
8

An rmANOVA on the entire dataset with laser as between groups factor and time and frequency as within groups factors revealed a significant interaction between group and time (Greenhouse Geisser: $F = 3.4$, $df = 6.8$, $p = 0.011$), between group and frequency (Greenhouse Geisser: $F = 2.9$, $df = 8.6$, $p = 0.015$) and finally between time and frequency (Greenhouse Geisser: $F = 19.6$, $df = 4.3$, $p < 0.001$) indicating that the effect of the laser was different for each group, but also dependent on frequency. Across groups, the course of this increase was significantly different (rmANOVA) with laser as between factor and both time and frequency as within factors (Greenhouse Geisser: $F = 2.4$, $df = 17.1$, $p = 0.005$). Close inspection of the Figure shows that we can interpret this as follows: the effect of laser treatment is larger at higher frequencies and is dependent on the type of laser used.

Differences between prelaser - directly postlaser and prelaser - late postlaser respectively were calculated. RmANOVA with laser as between factor and time as within factor and post-hoc analysis for these differences showed that the Thulium laser significantly increased thresholds compared to the Control group (Bonferroni: p = 0.015). The KTP laser was the only laser significantly less damaging than the Thulium laser (Bonferroni: p = 0.041; Dunnett: p = 0.003). For 16 kHz, the threshold differences of the CO_2 and Thulium groups were significantly increased compared to the Control group (Dunnett: Thulium, p = 0.001; CO_2, p = 0.015).

Latencies of the P_1 peak of the CAP at 16 kHz stimulation and 63 dB SPL are shown in **Figure 5**. This level was chosen because meaningful latencies can only be measured when a CAP actually occurs and at higher levels ceiling effects can occur (e.g., in **Figure 3** the KTP and the Diode laser). An rmANOVA with laser as between groups factor and time as within factor revealed a significant interaction of laser and time ($F = 24.5$, $df = 1.6$, $p < 0.001$).

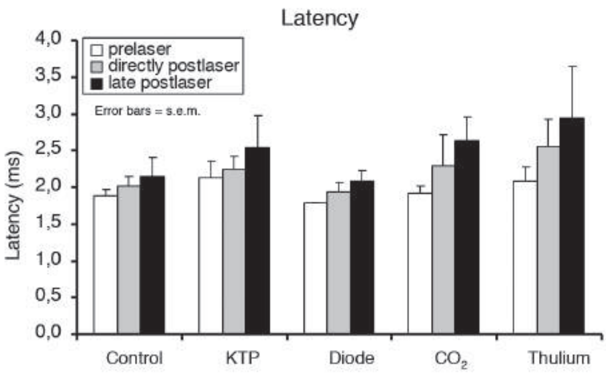

Figure 5 Latency
For each control and laser groups, latencies of the P1 peak of the CAP at 16 kHz stimulation and 63 dB SPL are shown. Latencies are shown before creating the cochleostomy (“prelaser”), directly after (“directly postlaser”) and 4 hours later (“late postlaser”). Error bars represent standard error of means (s.e.m.)

Discussion

The aim of these animal experiments was to gain more information on the safety of various laser systems used in stapedotomy. As a model, the basal turn of the guinea pig cochlea was chosen, because it resembles the human stapes footplate in structure and thickness.[13,20] In order to assess damage, we measured CAPs to evaluate inner ear function.

In summary, we found that the damaging effects of laser treatment are frequency dependent, with the largest effects at the highest frequency we measured (16 kHz). If we assess the effects on threshold at 16 kHz (**Figure 4**), we can order the different groups according to their damaging effect as follows: Thulium > CO_2 > Diode ≈ KTP > Control.

There seems to be a relation between the damage we measured and the way laser energy is absorbed in perilymph and more solid structures in the cochlea. For KTP and Diode lasers it was to be expected that damage predominantly occurs locally, because their energy will only limitedly be absorbed in the perilymph. Most energy will be absorbed at vascularized structures behind the perforation, like the basilar membrane, causing direct damage to neuro-epithelial cells. The minimal threshold changes we saw in Diode and KTP occurred at 16 kHz. When taking into consideration the tonotopic arrangement of the guinea pig cochlea, this is approximately the location of the fenestration. Sixteen kHz is the specific frequency for the location approximately 4 mm from the oval window, and centrally located in the basal turn.[21] In contrast, we see a more generalized shift in frequency dependent thresholds for the Thulium and CO_2 laser. These laser wavelengths are strongly absorbed in the perilymph, causing heating.[5,6,22] Since the volume of the cochlea is small, heating will spread quickly, potentially causing a shift in thresholds in surrounding frequencies. Earlier research, visualizing thermal effects in the vestibule, showed CO_2 laser energy is absorbed very quickly, giving temperature rise very locally. In contrast, in these experiments Thulium laser energy penetrated the vestibule for 1 to 2 mm, before it was absorbed.[5] This deeper heating might be related to the observed damage to a larger area in the present experiment.

When threshold shifts occur due to heating, there is a possibility that these threshold shifts are temporary and might recover over time. Possible recovery can occur in weeks. Previous research by Jovanovic et. al., showed a (partial) recovery of CAPs after 7 days, in guinea pigs treated with high power pulses of CO_2 laser.[20] Ren et. al. showed the same recovery in auditory brainstem responses (ABRs) after CO_2 laser application in the guinea pig cochlea.[23] Both authors found only limited threshold shifts, when lower (corresponding to clinical) settings were used. In long-term follow-up (6 months), minor degrees of hearing loss, up to 15 dB were reversible, higher degrees remained permanent.[11]

It needs to be said that the stimuli used in the experiments described above were broad band acoustic stimuli. We used small band, frequency specific stimuli, therefore measuring different parts of the cochlea independently. When the observed effects occur more locally, they might be overlooked when using a broad spectrum stimulus, therefore underestimating true and clinically relevant effects.

In laser-assisted stapedotomy in humans, local effects will not occur in the cochlea, but in the vestibule, located just behind the stapes footplate. Several authors have reported (transient) vertigo following KTP or Argon laser stapedotomy in patients, ranging from 6.6 to 39%.[17,24-26] No shift in bone conduction thresholds has been described. For CO_2 laser, a (mainly temporary) threshold shift in higher frequencies has been described, in early postoperative bone conduction thresholds.[27-29] Comparing this with our results, this might be explainable by the heating of the fluids in the vestibule, which communicates with cochlear contents.

Comparing the four lasers, we must conclude that KTP, Diode and, though slightly less, CO_2 laser systems seem safe to use for stapedotomy. The effects on hearing thresholds are small and may be temporary. With the Thulium laser, the threshold shifts are larger and more broadly spread across frequencies. Potential irreversible harm to inner ear function with the Thulium laser can not be excluded.

Conclusion

Laser-assisted cochleostomy in the guinea pig shows deterioration in amplitudes and prolonged latencies of CAPs, especially in the high frequencies. For KTP and Diode laser, threshold shifts are small and occur locally at the site of perforation, at approximately 16 kHz. CO_2 laser shows a threshold shift over a larger area, but changes are still small. Thulium, however, shows larger thresholds shifts broadly spread over the different frequencies. Therefore this laser is potentially harmful, when used in clinical cases of stapedotomy.

Acknowledgements

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chapter
8

9

A Nonrandomized Comparison of the Thulium laser and the CO_2 laser in Primary Stapedotomy for Otosclerosis

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Abstract

Objective: Comparing hearing results in patients with otosclerosis treated with laser-assisted stapedotomy, using the 2 µm Thulium laser or the CO_2 laser.
Study design: Prospective nonrandomized clinical study
Setting: In a tertiary referral center in France (Jean Causse Ear Clinic, Béziers) 208 primary stapedotomies were performed in 204 patients between March 2008 and November 2009. Sufficient follow-up data was available for 194 procedures.
Methods: The fenestration in the footplate was made with the Thulium laser in 98 procedures and with a flexible CO_2 laser in 96 procedures. Preoperative and postoperative audiometric results were compared. Side effects, such as vertigo and tinnitus were scored.
Results: Patients treated with the CO_2 laser, had better hearing outcome compared to the Thulium laser, at both 3 months and 12 months follow up. At 3 months, the success of the surgery, defined as a closure of the air-bone gap to within 10 dB, was 90.0% in the Thulium group, compared to 96.8% in the CO_2 group. Bone conduction shift showed an overall deterioration of 1.6 dB (SD 6.9) in the Thulium group compared to an improvement of 1.4 (SD 4) in the CO_2 group. In the Thulium group there were 4 patients with SNHL (4.4%) and 3 with tinnitus (3.1%), compared to none in the CO_2 group.
Conclusion: Stapedotomy surgery performed with a fiber-delivered Thulium laser resulted in a higher chance of inner ear damage measured by bone conduction shift, compared to the use of a fiber-delivered CO_2 laser. We advise not to use the Thulium laser for stapedotomy.

Introduction

Perkins introduced the Argon laser stapedotomy in 1980; using the Argon laser to perforate the footplate.[1] In comparison to conventional techniques, the application of lasers during a stapedotomy minimizes the risk of mechanical trauma to the middle and inner ear.[2] Multiple types of lasers have been suggested for use in stapes footplate fenestration, with wavelengths both in visible and invisible spectra, each with different characteristics. It remains unknown which laser has the best characteristics to be used for footplate perforation during stapedotomy surgery.[3] A recent systematic review showed a slightly better result regarding air-bone gap closure in favor of the CO_2 laser compared to the KTP laser.[2] However the clinical relevance of this small difference remains unclear. It is unknown how other, especially newer, laser types compare to the CO_2 laser.

The Thulium (continuous wave, $\lambda \approx 2$ µm) laser has become readily available in many hospitals, because of its frequent application in urology. It is often used for the minimally invasive treatment of benign prostate hyperplasia.[4-6] Quite similar to the CO_2 (continuous wave, $\lambda = 10.6$ µm) laser, the Thulium wavelength is strongly absorbed in water. Hence, the possible advantages of the CO_2 laser might also be applicable to the Thulium laser. Furthermore, a potential advantage of the Thulium laser is that it can be applied by using a very thin flexible silica fiber, instead of the slightly rigid hollow wave guide fiber that is currently necessary to allow CO_2 laser delivery.[7]

Although both lasers are absorbed well in watery fluids, the CO_2 laser is even more effectively absorbed compared to the Thulium laser. This means that energy absorption (heat production) for the CO_2 laser, when passing through the footplate, occurs right at the surface beneath the footplate resulting in minute amounts of water vapor.[8,9] The CO_2 laser will not penetrate any further than 0.3 mm (at the power levels used in ear surgery).[8] The Thulium laser, due to its lesser absorption, has its energy absorption reaching deeper below the footplate. It is reported that the Thulium laser penetrates up to approximately 1 mm before full absorption occurs.[8] In our own recently published study using thermal and mechanical imaging in an inner ear model, we could demonstrate potentially harmful water vapor bubbles occur with the Thulium laser due to its absorption characteristics.[9] Clinical data on the Thulium laser, compared to the CO_2 laser, have not yet been reported. The purpose of this prospective nonrandomized cohort study is to determine the safety and efficacy of the Thulium laser compared to the hollow waveguide-delivered CO_2 laser in patients undergoing primary stapedotomy surgery for otosclerosis.

Material and Methods

Patients

All patients treated between March 2008 and November 2009 were included in this prospective cohort study and were operated on by the same surgeon (R.V. at the Jean Causse Ear Clinic) using the same technique (primary stapedotomy with vein graft interposition) as previously described.[10] A total of 204 patients underwent 208 primary stapedotomies. Patients were divided in 2 groups according to the type of laser used for fenestration of the footplate; the Thulium laser was used in 104 procedures and another 104 procedures were performed using the CO_2 laser. Patients with obliterative otosclerosis and/or simultaneous malleus ankylosis or superior canal dehiscence were excluded. Obliterative otosclerosis was defined as the presence of hard, new bone filling the oval fossa, requiring an oval window drill out. This affected 3 patients in the Thulium group and 1 in the CO_2 laser group. In the Thulium group one patient was diagnosed with a superior canal dehiscence, when a CT scan was made after the conductive hearing loss remained after surgery.

Hearing status was assessed both before and 3 months after surgery. Available long term follow-up after 1 year was also assessed, in accordance with the Guidelines of the Committee on Hearing and Equilibrium.[11] Two patients in the Thulium group and 7 patients in the CO_2 group did not have an audiogram at either of these two endpoints and were excluded from the analysis. This resulted in the inclusion of 98 procedures in the Thulium group and 96 procedures in the CO_2 group for final analysis.

All data were tabulated using the Otology-Neurotolgy Database (ONDB) (AS Multimedia Inc., Cassagne, France).[10] This is a commercially available software package developed at the Jean Causse Ear Clinic, designed to comply with the American Academy of Otolaryngology guidelines for reporting clinical and audiometric results.[11]

Surgery

All procedures were performed by the same surgeon (R.V.). In all cases, a transcanal procedure was undertaken and laser stapedotomy was performed by using either the CO_2 laser or the Thulium laser, followed by a veingraft interposition. Patients were not randomized in groups, but treated in 4 blocks, depending on the availability of the Thulium laser. The surgical technique was similar in both groups and was described in more detail in a previous publication.[10] A rosette was created in the footplate of the stapes with the laser. The remaining bone was removed with a Skeeter microdrill (0.7 mm diamond dust burr). Routinely a 0.4-mm-diameter Teflon prosthesis of appropriate length was placed.

A 2 µm continuous wave ('Thulium') laser was used, coupled to a 365 µm silica fiber. Single pulses were used at 4-7W at 100 ms. A 10.6 µm continuous wave CO_2 laser (Omniguide Inc, Cambridge, MA, USA) was used. The light was delivered by a 3rd generation Omniguide Hollow Wave Guide (Beam-Path OTO-S, 250 µm, Omniguide, Cambridge, MA, USA). A flow of Helium gas was delivered through the centre of the fiber (> 1 bar) to prevent pollution of the fiber core. Single pulses were used at 4W (comparative to a 2W output) and 100 ms.

Audiometric assessments

Audiometric evaluation included preoperative and postoperative air-bone gap (ABG), air conduction (AC) thresholds and bone-conduction (BC) thresholds. Pure-tone averages (PTAs) were calculated over 4 frequencies; 0.5, 1, 2 and 4 kHz. AC and BC PTAs obtained at the same time postoperatively were used for calculation of ABG closure. The audiometry was reported according to the American Academy of Otolaryngology-Head and Neck Surgery Guidelines[11], except for the thresholds of 3 kHz, which were substituted in all cases with those at 4 kHz.

Audiometric evaluation was divided in early and late postoperative results. Early or short-term follow-up was defined as 2 to 4 months of follow-up. Long-term follow-up was defined as a follow-up duration of more than 12 months after surgery.

Success was defined as a postoperative ABG of 10 dB or less. Sensorineural hearing loss (SNHL) was defined as a change in BC PTA of 15 dB or more. Side effects, such as vertigo and tinnitus, were routinely checked at evaluation moments. Individual audiometric results were presented using Amsterdam Hearing Evaluation Plots (AHEPs).[12]

Statistical Analyses

Differences and 95% confidence intervals (95% CI) were calculated. Pre- and postoperative audiometric results were compared for the Thulium and CO_2 group, using an independent samples *t*-test. Pre- and postoperative proportions of success, postoperative SNHL and postoperative tinnitus were compared for the Thulium and CO_2 group, using a chi-squared test.

Results

Patient characteristics

In total, 98 procedures in the Thulium group and 96 procedures in the CO_2 group had an audiometric assessment between 2 and 4 months of follow-up and/or 12 months of follow-up available. **Table 1** shows the preoperative patient characteristics as well as preoperative audiometric parameters, with differences and 95%CIs. When presented differences are positive, this favors the Thulium group. When presented differences are negative, this favors the CO_2 group. None of the variables in the preoperative characteristics were significantly different between the 2 treatment groups. In the Thulium and CO_2 group, respectively 66.3% and 66.7% were female patients. Mean age was 49.0 years (standard deviation [SD] 11.4) and 48.4 years (SD 11.0) respectively. All patients were older than 18 years (**Table 1**).

Preoperative audiometric evaluation was similar in both groups. There was no significant difference in thresholds. The mean AC threshold was 47.7 dB (SD 10.3) in the Thulium group and 47.4 dB (SD 12.4) in the CO_2 group. Mean BC threshold was 20.8 dB (SD 8.1) and 21.4 dB (SD 8.9), respectively. Both AC and BC thresholds did not differ significantly between the two treatment groups with risk differences of 0.3 dB (-2.9 to 3.5) for mean AC and -0.6 dB (-3.0 to 1.9) for mean BC.

Table 1 Preoperative patient characteristics

Variable	Thulium laser n= 98	CO_2 laser n= 96	Difference (95% CI)
Age in yrs ((SD) min-max)	49.0 ((11.4) 21-74)	48.4 ((11.0) 19-70)	0.5 (-2.6 to 3.7)
Sex (% female)	66.3	66.7	-0.3 (-13.6 to 12.9)
Mean BC, dB (SD)	20.8 (8.1)	21.4 (8.9)	-0.6 (-3.0 to 1.9)
Mean AC, dB (SD)	47.7 (10.3)	47.4 (12.4)	0.3 (-2.9 to 3.5)
Mean ABG, dB (SD)	26.9 (6.9)	26.0 (7.2)	0.9 (-1.1 to 2.9)
BC at 0.5 kHz, dB (SD)	13.5 (5.9)	14.0 (6.0)	-0.4 (-2.1 to 1.3)
BC at 1 kHz, dB (SD)	18.0 (8.1)	19.1 (8.5)	-1.1 (-3.4 to 1.3)
BC at 2 kHz, dB (SD)	25.6 (10.9)	26.5 (12.4)	-0.9 (-4.2 to 2.4)
BC at 4 kHz, dB (SD)	26.1 (13.1)	25.9 (14.0)	0.2 (-3.7 to 4.0)
AC at 0.5 kHz, dB (SD)	50.5 (9.7)	48.7 (11.1)	1.8 (-1.1 to 4.8)
AC at 1 kHz, dB (SD)	50.6 (10.5)	50.0 (11.6)	0.6 (-2.5 to 3.7)
AC at 2 kHz, dB (SD)	45.1 (12.5)	45.9 (14.8)	-0.8 (-4.7 to 3.0)
AC at 4 kHz, dB (SD)	44.5 (16.3)	44.8 (18.7)	-0.4 (-5.3 to 4.6)

n = number of procedures, BC = bone conduction, AC = air conduction, ABG = air-bone gap, SD = standard deviation, CI = confidence interval. Means were calculated using BC and AC thresholds at 0.5, 1, 2 and 4 kHz

Postoperative Audiometric assessment at 3 months follow-up

For 90 procedures in the Thulium group and 93 procedures in the CO_2 group, there was an audiometric assessment between 2 and 4 months follow up available. Short-term follow-up was therefore achieved in 94.3% of the 194 procedures that were included. The mean follow-up duration was 3.3 months (SD 0.6) for the Thulium group and 3.4 months (SD 0.5) for the CO_2 group. Results of the audiometric evaluation and possible side effects, namely SNHL, vertigo and tinnitus, are shown in **Table 2.**

Table 2 Hearing results at 3 months follow-up

Variable	Thulium laser (n= 90)	CO_2 laser (n= 93)	Difference (95% CI)
Mean follow up in months (SD)	3.3 (0.6)	3.4 (0.5)	-0.04 (-0.2 to 0.1)
ABG ≤10 dB (%)	90.0	96.8	-6.8 (-13.9 to 0.4)
Mean BC, dB (SD)	22.8 (10.8)	20.2 (8.6)	2.5 (-0.3 to 5.4)
Mean AC, dB (SD)	27.4 (11.8)	23.4 (8.6)	4.0 (0.8 to 7.2)*
Mean ABG, dB (SD)	4.6 (4.5)	3.1 (4.0)	1.5 (0.2 to 2.7)*
Mean change in BC, dB (SD)	-1.6 (6.9)	1.3 (4.0)	-2.9 (-4.6 to -1.2)*
Mean change in AC, dB (SD)	20.7 (9.8)	24.0 (9.2)	-3.3 (-6.0 to -0.5)*
Mean change in ABG, dB (SD)	22.3 (7.1)	22.7 (7.1)	-0.5 (-2.5 to 1.6)
SNHL (%) >15 dB	4.4	0	4.4 (0.2 to 8.7)*
Vertigo (%)	0	0	-
Tinnitus (%)	3.1	0	3.1 (-0.3 to 6.5)

n = number of procedures, BC = bone conduction, AC = air conduction, ABG = air-bone gap, SD = standard deviation, CI = confidence interval. Means were calculated using BC and AC thresholds at 0.5, 1, 2 and 4 kHz. SNHL= sensorineural hearing loss, defined as a change in BC PTA of 15 dB or more.

* **P**-value < 0.05

The success of the surgery, defined as a closure of the ABG within 10 dB, was 90.0% in the Thulium group, compared to 96.8% in the CO_2 group. The risk difference (-6.8%) was not significant, with a 95% CI ranging from -13.9 to 0.4. Mean postoperative AC, mean postoperative ABG and mean change in AC were significantly better in the CO_2 group (differences of 4.0 dB (95% CI 0.8 to 7.2), 1.5 dB (95% CI 0.2 to 2.7) and -3.3 dB (95% CI -6.0 to -0.5) respectively). The mean BC deteriorated by 1.6 dB (SD 6.9) in the Thulium group compared to an improvement of 1.3 dB (SD 4.0) in the CO_2 group, which is significantly different (-2.9 dB (95% CI -4.6 to -1.2)). Moreover there were no patients in the CO_2 group with postoperative SNHL or tinnitus, whereas in the Thulium group there were 4 patients with SNHL (4.4%) and 3 with tinnitus (3.1%).

The individual hearing results at 3 months follow up are depicted in Amsterdam Hearing Evaluation Plots (AHEPs). In **Figure 1**, the effects of surgery on BC, for each individual ear, are visualized (AHEP I). The 2 diagonal lines enclose an area in which the BC did not change 10 dB or more. The area under the curve represents an improvement of BC of more than 10 dB: a large overclosure. Above the dotted line, the procedures are represented with a BC deterioration of more than 10 dB. The 4 procedures in this area were all ears where surgery was performed with the use of the Thulium laser. In the second AHEP, depicted in **Figure 2**, gain in AC is plotted against preoperative ABG. Procedures located on the solid line, represent a total closure of ABG. Procedures in the area enclosed by the solid and dotted line, showed an ABG closure to within 10 dB and are considered successful surgeries. Below the solid line, we can see the cases of overclosure, which is more common in procedures performed with the use of the CO_2 laser. In the area above the dotted line, the change in AC was insufficient to close the preoperative ABG to within 20 dB. The 3 procedures that are located left from the y-axis, represent cases with a large BC shift, thereby lowering AC thresholds.

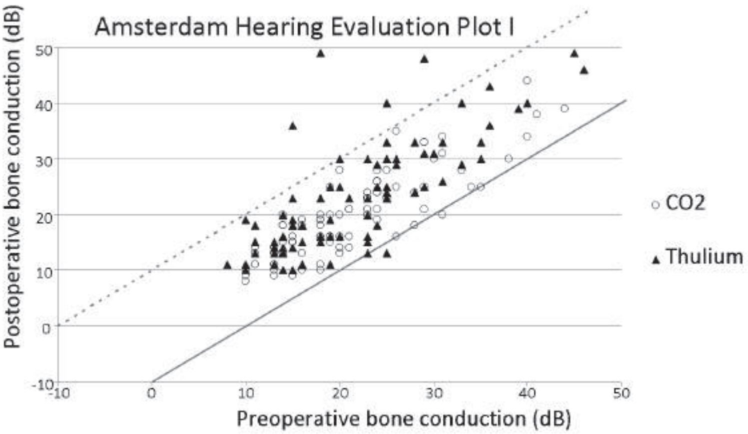

Figure 1 Amsterdam Hearing Evaluation Plot I at 3 month follow up
Postoperative bone conduction thresholds plotted as a function of preoperative bone conduction thresholds

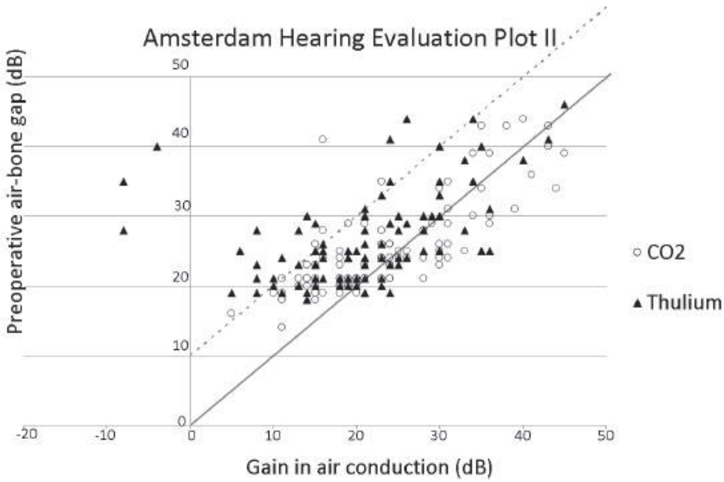

Figure 2 Amsterdam Hearing Evaluation Plot II at 3 month follow up
Postoperative gain in air conduction thresholds plotted against the preoperative air-bone gap
The area between the diagonal lines represents successful surgery, with an ABG closure to within 10 dB

Postoperative Audiometric assessment at >12 months follow-up

For 60 procedures in the Thulium group and 57 procedures in the CO_2 group, there was a follow-up moment at more than 12 months' time (60% of 194 procedures). Because many of these patients have to travel long distances to visit the department, onsite follow-up care is sometimes not possible.

Success of the surgery after 1 year, defined as ABG to within 10 dB, improved slightly to 93.3% in the Thulium group and to 100% in the CO_2 group (see **Table 3**). The risk difference for ABG closure to within 10 dB between the two treatment groups was significant (-6.7 (95% CI -13.0 to -0.4)). Mean BC and mean AC were both significantly better for the CO_2 group (differences of 2.9 dB (95% CI 0.1 to 5.7) and 4.3 dB (95% CI 1.0 to 7.7) respectively). The significant difference in change in BC, as seen at 3 months follow-up, remained present at long-term follow-up (-3.4 dB (95% CI -5.4 to -1.4)).

Table 3 Hearing results >12 months follow-up

Variable	Thulium laser (n= 60)	CO_2 laser (n= 57)	Difference (95% CI)
Mean follow up in months (SD)	19.5 (9.6)	19.3 (9.3)	0.2 (-3.3 to 3.7)
ABG ≤10 dB (%)	93.3	100	-6.7 (-13.0 to -0.4)*
Mean BC, dB (SD)	22.0 (8.2)	19.1 (6.9)	2.9 (0.1to 5.7)*
Mean AC, dB (SD)	26.0 (10.1)	21.7 (7.6)	4.3 (1.0 to 7.7)*
Mean ABG, dB (SD)	4.0 (6.9)	2.5 (2.6)	1.4 (-0.5 to 3.3)
Mean change in BC, dB (SD)	-1.8 (5.7)	1.6 (5.3)	-3.4 (-5.4 to -1.4)*
Mean change in AC, dB (SD)	19.8 (12.0)	23.1 (9.8)	-3.4 (-7.4 to 0.7)
Mean change in ABG, dB (SD)	23.4 (10.1)	22.5 (5.9)	0.9 (-2.1 to 3.9)

n = number of procedures, BC = bone conduction, AC = air conduction, ABG = air-bone gap, SD = standard deviation, CI = confidence interval. Means were calculated using BC and AC thresholds at 0.5, 1, 2 and 4 kHz.
* **P-**value <0.05

Discussion

The present study clearly shows differences in hearing outcome after laser-assisted stapedotomy with the use of Thulium and CO_2 laser. The success rates of the surgery, defined as an ABG closure to within 10 dB, is lower in patients treated with the Thulium laser, both at 3 months follow-up and long-term follow-up of 12 months or more. Moreover, there is a significant change in BC threshold, with an increased risk of substantial SNHL and development of tinnitus in the Thulium laser group. Thulium laser seems more harmful to inner ear function compared to the CO_2 laser. The question is why this laser is more damaging to the delicate inner ear, compared to other lasers.
Research in an inner ear model, comparing heating patterns between KTP, CO_2 and Thulium laser, revealed more heating after fenestration of the footplate with the Thulium laser.[8] Objective measurement of heating below the footplate, captured by an infrared Thermo camera showed a temperature shift of 9.4°C (SD 6.9) in the area of 2 mm below the footplate.[8] An overall temperature rise over 4 °C is considered harmful. Animal studies have shown that stable inner ear function is maintained if the perilymph temperature raises no more than 3 °C. Further heating of the perilymph results in reversible damage and prolonged heating to irreversible changes.[13,14] High-speed imaging of the mechanical

effects in the vestibule showed the formation of water vapor bubbles in the vestibule both for the CO_2 and Thulium laser. The bubbles were larger in the Thulium experiments, causing pressure waves when imploding.[9] Potentially these mechanical effects might even be more damaging to inner ear function than the thermal effects.
In an animal model using guinea pigs, hearing thresholds deteriorated the most after using the Thulium laser for cochleostomy, compared to KTP, Diode and CO_2 laser.[15] Functional outcomes in patients have not been reported previously in large study populations. Barbara et al. described functional outcomes of 10 patients who underwent a classical stapedotomy with the use of the Thulium laser. Four patients (40%) had postoperative complications, such as vertigo and tinnitus.
In this study, the use of the Thulium laser resulted in a BC hearing deterioration with an average of 1.6 dB (SD 6.9) at short-term follow-up. There were 4 patients with a BC shift of more than 15 dB, which is more concerning. This SNHL is irreversible and a major disappointment for both the patient and the surgeon. Substantial damage to the inner ear occurred in these cases. It is interesting to note that none of these patients reported postoperative vertigo. Damage to the inner hair cells, due to thermal or mechanical effects, should also influence vestibular function. Especially since the vestibule is located directly after the stapes footplate. It is possible that patients do underreport (transient) vertigo.
Several limitations of this study need to be taken into account. Since we did not perform a randomized controlled trial, selection bias cannot be completely precluded. It is also important to note that long-term follow-up of more than 12 months was not available for all of the patients treated between March 2008 and November 2009. Selective loss to follow-up may lead to selection bias and an under- or overestimation of treatment effects. Patients did not report for long-term follow-up because of travel distances. It is to be expected that patients are more likely not to return for follow-up visits if the results of the surgery were satisfactory. If selective reporting was an issue, underestimation of treatment effects could be expected instead of an overestimation.

Conclusion

Stapedotomy surgery performed with the Thulium laser resulted in a higher chance of inner ear damage, compared to the CO_2 laser. Based on the results of the present study, the application of the Thulium laser for stapedotomy surgery should not be advised.

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10

General Discussion

When a patient decides to undergo a stapedotomy for otosclerosis, he or she will expect hearing improvement without substantial side effects, such as tinnitus or vertigo. It is up to the surgeon to explain possible risks of the procedure and to try to make sure that these risks are as small as possible. Risk minimization greatly depends on the chosen surgical technique. For instance, making a fenestration in the stapes footplate, rather than removing the entire footplate, reduces the chance of perilymph leakage[1] and, thereby reducing the chance of complications. Traditional, micropick instruments or microburrs were used to make the fenestration. This technique entails substantial mechanical energy, which may cause SNHL or other complications.
The introduction of lasers in otology was believed to be safer, without or with very limited side effects, since they allow for a non-contact method. Nonetheless, laser use is associated with side effects, as a result of heating, mechanical and acoustic effects. Therefore, a comparison between lasers would help to make an evidence-based decision regarding the choice of the laser and eventually improve patient outcomes.
In this thesis four different lasers were compared. This general discussion will focus on different topics of debate, the final choice for laser and some practical tips for surgeons.

Does our inner ear model sufficiently represent the real inner ear?
In **chapters 4, 5 and 6** an inner ear model is used to visualize processes occurring in the vestibule during laser fenestration of the stapes footplate. A suitable model should closely mimic the anatomical and physiological situation. In addition, it has to be possible to place the model in an imaging setup. Important components of the model are the following:

1) Stapes

To mimic bone ablation processes and side effects during stapedotomy, the quality of bone should match that of a human stapes. Therefore, the use of an human cadaver stapes seems to be a logical choice. Fresh frozen human cadaver stapes were preferred over those preserved in formaldehyde, since this chemical causes dehydration of the bone. The dehydration process might influence the results, especially in lasers that are characterized by a high absorption rate in water, such as CO_2 and Thulium laser.

2) Proportions of size

The vestibule is located directly underneath the stapes footplate. The depth of the vestibule is around 3 mm. By using a polyacrylamide gel, the vestibule shape could be reproduced. Then, the artificial vestibule was filled with 0.9% NaCl, resembling perilymph. A hydrophone was incorporated in our inner ear model to measure acoustic effects and pressure waves. The polyacrylamide gel can conduct acoustics and pressure waves, making it possible to measure these effects.

3) Transparent

For the imaging set up a transparent model is required. Both the polyacrylamide gel as well as the 0.9% NaCl are transparent. Two very thin glass plates are used to sandwich the slab of gel. These glasses are placed in a plastic holding container. It is thus possible to observe what happens in the artificial vestibule during the experiments.

However, this model has some limitations. Since the border of the vestibule is flexible, expansion is possible. This could result in the overestimation of bubble formation and an underestimation of pressure waves[2]. Secondly, the borders of the human vestibule consist of highly vascularized neuro-epithelium. Absorption of laser wavelengths in these pigmented areas occurs when using the KTP laser. Unfortunately, our artificial vestibule comprises a non-pigmented gel. The question is whether absorption occurs at the borders of this non-pigmented gel. Thus, in order to be as close as possible to the in vivo situation, a cherry colored dye is used to pigment the artificial vestibule in the KTP laser experiments.

Would it be better to use an objective measurement of heating instead of comparing heating patterns?

In **chapters 4 and 6** the results of the high speed Schlieren imaging is shown. This technique compares the thermo dynamics of the different lasers by visualizing temperature gradients. The data is qualitative instead of quantitative.[3] The different colors in the imaging, can not be translated to absolute temperatures. A quantitative outcome, such as an exact temperature change, might instigate the feeling of a more objective or a more reliable measurement. The opposite appears to be true. Objective measurements are a challenge in these small inner ear models.

Thermocouples, mostly used for the quantitative measurement of heat, only measure heat at one distinct point. The placement of the thermocouples is therefore essential. Also size and material of the thermocouple can influence the outcome of the measurements. Direct illumination of thermocouples by lasers make results unreliable due to artifacts. Therefore, the data of studies using thermocouples differ greatly.[4-6] These limitations make thermocouples not ideal for measuring heat, especially when the area of heating is small and exposure time is limited.

Another possibility is the use of a thermo camera for measuring absolute temperatures. A thermo camera captures infrared (IR) radiation from a surface and absolute temperatures can be deducted from these images. One of the major advantages of this technique is the possibility of capturing the changes in heat over a longer period of time. The main drawback of this technique is the inability to measure heat below the surface. In a temporal bone the thermo camera would only capture the IR radiation from the bone surrounding the fenestration. However, we are much more interested in the temperature rise of the perilymph underneath the footplate. We used the IR camera to measure superficial heating below the footplate in the polyacrylamide gel seen from the side view. Unfortunately, this technique cannot measure heat in liquid directly under the footplate as water itself blocks all IR light. As the CO_2 wavelength is in the IR spectrum, this technique cannot be used for this laser; it would overexpose and even damage the IR camera.

The main advantage of the high speed Schlieren Imaging is that it enables us to view relative temperature changes at high speed (down to milliseconds). This provides a good insight in the thermodynamic processes occurring inside the inner ear which can be used to predict potential damage to inner ear function.

What do these mechanical effects seen in the vestibule mean?

In **chapters 5 and 6** the results of regular high speed imaging of the different lasers are shown. Previous research on laser effects has always focused on heating in the perilymph and acoustic effects. In the mentioned chapters, substantial differences between lasers and their mechanical effects are shown. Not only bubble formation is observed, but also pressure waves and flow through the perilymph are detected. Since these effects have not been described earlier, a question about their meaning and their potential to damage the inner ear structures arises. It may be possible that the side effects of stapedotomy, such as vertigo, tinnitus and SNHL, might be a result of the mechanical effects occurring in the vestibule, rather than the thermal effects. High speed fluid motion might locally induce shear stress on the neuro-epithelial cells in vestibular wall.

Further research in this field is required for a better understanding of these mechanisms. An inner ear set up, solely focusing on these mechanical effects, with better visualization techniques of pressure waves and flow, might increase our knowledge in this subject.

Why use the cochleostomy in the guinea pig as a model for stapes surgery?

In **chapters 7 and 8** a laser-assisted cochleostomy in guinea pigs, as a model for stapes surgery, was performed. It might seem more logical to do a stapedotomy in the guinea pig, rather than a cochleostomy. Unfortunately, the stapes footplate is rather hidden behind the fused malleus-incus complex and the facial nerve. This makes it difficult to access the stapes footplate. Moreover, the proportions of the stapes and vestibule differ in the guinea pig. The stapes is smaller and thinner, and the vestibule more shallow, making it difficult to find resembling laser settings. Also, the effects on the vestibular organ are difficult to measure in an animal model.

Making a cochleostomy is a more appropriate model to answer our question regarding functional outcomes following laser use. As the thickness of the cochlear wall resembles stapes thickness in humans and the distance to the basilar membrane is equal to the depth of the vestibule, it is a better model. Also, it is possible to accurately measure outcome in hearing.

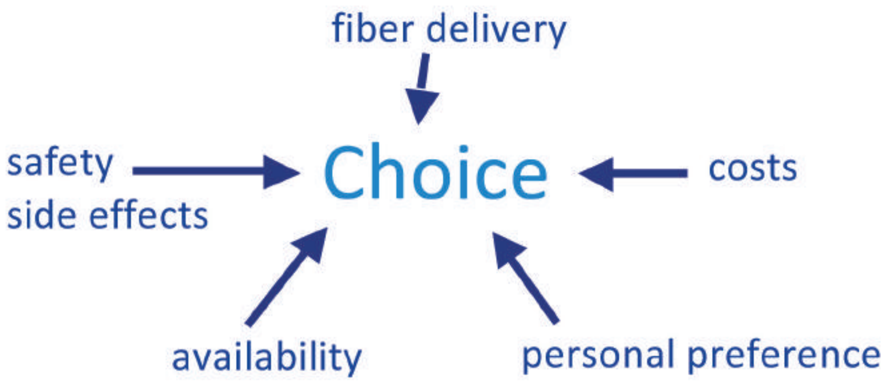
Can we draw any conclusions from the nonrandomized patient trial?

In **chapter 9** the results of a nonrandomized clinical trial comparing the Thulium laser to the CO_2 laser in primary stapedotomy for otosclerosis is shown. Although no randomization is performed, the two patient groups are comparable at the baseline. Hearing results are better for the CO_2 laser group. In the Thulium laser group there is deterioration in bone conduction (BC) and a significantly higher level of patients with a post-operative SNHL. These effects are likely to be explained by inner ear damage by the laser.

All patients in this trial are operated by the same surgeon applying the same surgical technique. The KTP and CO_2 laser have been compared earlier by the same surgeon.[7] A slight preference is found for the CO_2 laser over the KTP laser, as air bone gap (ABG) closure at 4 kHz is higher.

The question remaining is whether these results can be generalized over larger patient populations. One of our limitations is that all surgeries are performed by one surgeon. Possibly, the surgeons' preference for a laser can influence the outcome. It would be interesting to compare different lasers in a randomized controlled trial, where different surgeons perform the surgery. Tinnitus and vertigo questionnaires should be added to get a better insight in occurrence of these symptoms.

So which laser do we choose?



Finally, the following question remains: which laser should we choose for stapedotomy? The laser choice depends on different factors shown in **Figure 1**. In this thesis four different lasers in stapedotomy were tested and their safety issues are summarized in **Table 1**. The Thulium laser is clearly less safe. However, the KTP, Diode and CO_2 lasers all seem safe for stapedotomy. The eventual choice between these three lasers might be influenced by other factors, such as the possibility of fiber delivery, costs, availability and personal preference.

Delivery method

The use of a fiber is essential for the precise application of laser light in the small middle ear. The KTP, Diode and Thulium laser wavelength can easily be fiber delivered with the use of a silica fiber and a hand piece. In contrast, the CO_2 laser wavelength cannot be delivered through a silica fiber and needs a special hollow waveguide. Unfortunately, the use of hollow waveguides has several drawbacks. First, the hollow waveguides are vulnerable since they may break when they are subjected to over bending. Second, since the loss of energy over the waveguide is around 30-50%, higher inputs are usually required to ensure a good output. Further, the output can be affected by the curvature of the waveguide. Third, as the waveguides are hollow, there is a chance of particles entering the output zone of the fiber, possibly causing explosions in the tip of the fiber. To minimize this risk, a continue flow of helium through the fiber is advised. Last, the hollow waveguides are relatively expensive and cannot be re-sterilized.

Table 1 Comparing side effects, surgical preference and costs of the different lasers

	KTP **532 nm**	**Diode** **980 nm**	**Thulium** **2 µm**	**CO_2** **10.6 µm**
Side effects • Thermal effects	Hardly any	Hardly any	Extensive heating within vestibule	Superficial heating
• Mechanical effects	Plume formation in middle ear	Hardly any	Bubble formation	Microbubbles
• Acoustic effects*	Hardly any, low frequency 49 ± 8 dB(A)	Hardly any, low frequency 52 ± 8 dB(A)	Largest sound production, high frequency 68 ± 4 dB(A)	Some sound production, high frequency. Corresponding pressure waves with imploding microbubbles 83 ± 6 dB(A)
• Functional outcome	Minimal high frequency hearing loss	Minimal high frequency hearing loss	High frequency hearing loss	Minimal high frequency hearing loss
• Patient outcome	Comparable to CO_2	No large patient series yet	Significantly worse outcome compared to CO_2	Comparable to KTP
Surgical preference • Delivery method	Fiber delivered, handpiece	Fiber delivered, handpiece	Fiber delivered, handpiece	Hollow wave guide, or articulated arm with micromanipulator
• Practical	Carbonisation of the tip	Substantial carbonisation of the tip	Low bone ablating effects	True non-contact
Costs • Laser	€€	€	€€	€€
• Fiber	€€	€	€	€€€ (hollow wave)

* all lasers generate significantly less sound than a microburr; 95 ± 7 dB(A)

chapter 10

Practical aspects

Both the KTP and Diode laser need a substantial carbonization of the fiber tip to ensure bone ablation. This carbonization can vary over time, causing possible fluctuations in the output. A pre-coated laser tip ('black-tip'), as has been introduced in neurosurgical procedures, would be a possible solution.[8]

The KTP, Diode and Thulium lasers need contact of the fiber tip to the footplate. On the other hand, the CO_2 laser is a full non-contact device. By placing the hollow waveguide 1 mm from the footplate a perfect perforation can be achieved. The CO_2 laser has high bone ablating capacities and it does not need any form of carbonization.

Availability and costs

The use of a laser for stapedotomy might be more expensive than a traditional technique. Especially when switching to a laser, acquisition costs might influence the choice of the laser, although these costs can be shared when the laser is also used for other surgical procedures, in ORL or other specializations.

Once the laser is already available, costs will be made for maintenance of the laser and for the fibers.

The Diode laser is relatively inexpensive since it is a small battery driven. Thus, maintenance costs are low. Fibers are single use and relatively inexpensive as the hand piece can be detached and re-sterilized.

In KTP laser the current fibers are more expensive as they are single use and include the hand piece.

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11

Summary
Samenvatting

Summary

Otosclerosis is a disorder of the bone homeostasis of the otic capsule. The process usually starts in the oval window, fixating the stapes, resulting in a conductive hearing loss. A stapedotomy can be performed to restore hearing. During this surgery a small hole is created in the footplate of the stapes. In this fenestration a prosthesis is placed, which is connected to the incus, thereby regaining the mobility of the ossicular chain.
Stapedotomy is not without risks, especially when making the fenestration. Just underneath the footplate the vestibule, a part of the organ of equilibrium, is located. The fluid in the vestibule, the perilymph, is in direct contact with fluids of the cochlea. Damage to these inner ear structures can cause vertigo, tinnitus and hearing loss.
Traditionally, the fenestration in the footplate is made by a micropick instrument or a microburr. This contact technique entails substantial mechanical energy. These mechanical forces might cause damage to the delicate inner ear structures. A non-contact method, by using a laser, seems preferable. Nonetheless, the laser use is associated with side effects, as a result of heating, mechanical and acoustic effects.
The aim of this thesis is to explore the effects of different lasers used in stapedotomy in order to identify the best one.

Literature search
Since no complete literature overview was available on laser use in stapedotomy, a systematic literature search has been provided in **chapters 2 and 3.** In **chapter 2** hearing results of the conventional technique were compared to a laser-assisted stapedotomy and in **chapter 3** a comparison between different lasers was made. PubMed, Embase, the Cochrane Library, CINAHL and Scopus were searched to identify available evidence. Directness of evidence and risk of bias was assessed. Two authors assessed quality and extracted data independently.

In **chapter 2** the results of the review comparing conventional technique versus laser are presented. Twenty-one articles were identified through the search. Thirteen studies had to be excluded due to high risk of bias. Common bias was no standardization in treatment outcomes and high percentages of loss to follow up. Eight studies, all with moderate risk of bias, were included for the final analysis. This limited evidence, showed no consistent difference in post-operative ABG closure or immediate vertigo between groups. Both footplate fractures and SNHL, however, appears to occur more frequently in the conventional group than in the laser group. When this risk of harm is taken into account, the use of a laser is preferred over conventional methods for the footplate fenestration.

In **chapter 3** the results of the systematic review comparing hearing outcome using different lasers for stapedotomy are presented. Eight studies comparing two lasers in stapedotomy were identified and six of them were excluded 6 for the final analysis due to high risk of bias or low directness of evidence. Common bias was limited standardization of outcome. Finally we included two studies. Vincent et. al. compared CO_2 laser to KTP laser in a nonrandomized patient series.[1] He found a slightly better ABG closure for CO_2 laser. However, the clinical relevance is still unclear. Marchese et. al. compared Er-YAG to CO_2 laser and found a larger difference in favor of CO_2 laser in ABG closure.[2] Unfortunately, there is little evidence comparing different lasers. Thus, no definitive conclusions can be drawn on which laser to use for fenestration in stapedotomy, from literature review only.

Inner ear model

In **chapters 4, 5 and 6** an inner ear model with high speed imaging is proposed to capture effects occurring during laser fenestration of the footplate. This inner ear model consists of a slap of gel, with an artificially made vestibule filled with 0.9% NaCl. A human fresh frozen stapes is placed on top.

Effects occurring during laser fenestration can be predicted by the lasers' wavelength absorption in water. It is expected that laser wavelengths with high absorption in water and, therefore, in the perilymph, should show higher temperature rises compared to laser wavelengths that are only limited in their absorption in water. The CO_2 wavelength, 10.6 μm, has a high absorption in water. Immediately after entering the perilymph it should be absorbed, causing heat. The 532 nm KTP wavelength should barely be absorbed in the perilymph. It should penetrate until it reaches the borders of the vestibule, where absorption should take place in the pigmented areas of the neuro-epithelial cells. The 2 μm Thulium wavelength and the 980 nm Diode wavelengths should only partially be absorbed in the perilymph.

To study the thermal effects, a special optical technique was used based on color Schlieren imaging.[3] This technique visualizes non-uniformities in the refractive index of a transparent medium induced by, e.g., a temperature gradient. Light rays passing through water are deflected if a temperature gradient caused by laser induced heating is present. The non-deflected and deflected rays are focused onto a rainbow filter. This produces a colored "thermal" image, showing the presence and the dynamics of the temperature gradient in real time. With a high intensity white illumination source, frame rates up to 500 f/s can be obtained. This technique compares the relative local temperature changes. However, it does not show absolute temperatures.

In **chapters 4 and 6,** the results of the high speed Schlieren imaging are shown for the KTP, Diode, Thulium and CO_2 laser. With a single laser pulse on an intact footplate, we did not see any heating in the vestibule for the KTP and Diode laser. After fenestration with CO_2 laser, energy was absorbed very fast in the fluid of the vestibule, creating vapor bubbles from heated liquid (indicating temperatures >100 °C) in the vestibule during the pulse. The heating pattern occurred very local and cooled down rapidly. In the case of the Thulium laser, more extended thermal effects were observed up to 1 mm below the footplate. The heated area consisted of different colored rings, representing a steep temperature gradient.

Besides heating, mechanical effects can also occur in the vestibule during laser fenestration of the footplate. In the case of fast absorption vaporization bubbles can occur. Implosion of these bubbles can cause a shock wave. Acoustic effects can also occur during explosive ablation of bone. These mechanical and acoustic effects could damage the inner ear structures. Since these effects occur in very short timeframes, we used high speed imaging, with a frame rate up to 4000 f/s, to capture these effects which are invisible to the human eye. The sounds produced during the fenestration were recorded simultaneously with a hydrophone incorporated in the set-up.

In **chapters 5 and 6** the results of the mechanical and acoustic effects of the four lasers are presented. The KTP and Diode lasers showed little mechanical effects, with minimal sound production. When CO_2 laser was used, miniscule bubbles arose in the vestibule. Implosions of these bubbles corresponded to shock waves in the acoustic measurements. The Thulium laser imaging showed larger bubbles in the vestibule, with a sound production higher than the other lasers. However, each of these lasers generated significantly less noise than the conventional microburr.

Animal model

Theoretically, the KTP laser could be damaging to the inner ear, not due to heating or mechanical effects, but by penetration through the vestibule. The 532 nm wavelength would be barely absorbed in perilymph. When the laser light enters the vestibule, it would penetrate until it reaches the borders of the vestibule. As the neuro-epithelial cells here are highly vascularized, local absorption will occur at this level. Potentially this should directly damage these sensory cells.

In **chapter 7** the results of a pilot study in 6 guinea pigs are shown. In the guinea pig the cochlea is easily accessible by opening of the bulla. The thickness of the bone of the cochlea is comparable to the thickness of the human stapes bone. The distance to the delicate basilar membrane is approximately 3 mm, which is comparable to the depth of the vestibule.

In this study a cochleostomy was performed with the KTP laser, making 4 perforations in the cochlea. Normal clinical setting (1 W, 100 ms) were used, but also higher settings up to 5 W. In the histological preparations, we did not find any direct damage to the organ of Corti or the basilar membrane in light microscopy. We did see blood clots in vessels in the cochlear wall and substantial intrascalar blood in the scala tympani.

To answer the question whether the above mentioned effects could affect inner ear function, a comparison of the lasers was done. We measured acoustically evoked CAPs, as a function of the inner ear, after laser cochleostomy. The obtained results are shown in **chapter 8.**

A decrease in CAP amplitudes and an increase in CAP thresholds were found after cochleostomy with each laser. The increase in thresholds was significantly larger for higher frequencies. The Thulium laser evoked the largest threshold shifts and the KTP laser the smallest. The Diode and CO_2 laser were in intermediate positions. Threshold shifts were small over the different frequencies, although at 16 kHz the threshold was significantly increased for the Thulium and CO_2 lasers. It needs to be pointed out that our last measurement was 4 hours after laser cochleostomy. There is a possibility that these threshold shifts are temporary and might recover over time. Possible recovery can occur in weeks, especially in minor degrees of hearing loss. Previous research showed that losses of 15 dB or more (as seen with the Thulium and CO_2 lasers in our experiment) remained permanent.[4]

Patient series

In **chapter 9 t**he results of a nonrandomized comparison of the Thulium and CO_2 lasers in primary stapedotomy for otosclerosis are shown. We compared 98 procedures with the Thulium laser to 96 procedures performed with the CO_2 laser. Group characteristics were comparable; all patients were operated by the same surgeon applying the same technique. Follow up consisted of pure tone audiometry and was obtained at 3 months and after 12 months.

Patients treated with the CO_2 laser, had a higher success rate of the surgery (defined as an ABG closure <10 dB), compared to the Thulium group. Bone conduction shift showed an overall deterioration of 1.6 dB (SD 6.9) in the Thulium group, compared to an improvement of 1.4 dB (SD 4.0) in the CO_2 group. More concerning, in the Thulium group there were 4 patients with SNHL (4.4%) and 3 with tinnitus (3.1%) compared to none in the CO_2 group.

Conclusion

In this thesis a detailed overview is presented on the effects occurring in laser-assisted stapedotomy. Thulium laser shows a poor performance compared to KTP, Diode and CO_2 lasers in the inner ear model and animal model experiments. Further, in the patient series we see a higher percentage of patients with substantial SNHL and tinnitus compared to CO_2 laser. It is thus advisable not to use the Thulium laser in stapedotomy. The KTP, Diode and CO_2 lasers seem to be safe when used in stapedotomy.

To the surgeon

If you want to start using a laser in stapedotomy, please pay special attention to our '*tips for the surgeon'* section in the appendix.

References

1. Vincent R, Bittermann AJ, Oates J et al. KTP versus CO2 laser fiber stapedotomy for primary otosclerosis: results of a new comparative series with the otology-neurotology database. Otol Neurotol 2012;33:928-933.

2. Marchese MR, Scorpecci A, Cianfrone F et al. "One-shot" CO2 versus Er:YAG laser stapedotomy: is the outcome the same? Eur Arch Otorhinolaryngol 2011;268:351-356.

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Samenvatting

Otosclerose is een ziekte in de botaanmaak rondom het slakkenhuis. Dit proces begint meestal in het ovale venster, waardoor de stapes (of stijgbeugel) gefixeerd raakt. Hierdoor ontstaat er een conductief gehoorverlies. Om het gehoor te verbeteren, kan er een stapedotomie worden uitgevoerd. Tijdens deze ingreep wordt er een klein gaatje gemaakt in de voetplaat van de stapes. In deze fenestratie wordt een prothese geplaatst, die wordt vastgemaakt aan de incus, zodat er weer een bewegende gehoorbeenketen ontstaat.

Het uitvoeren van een stapedotomie, in het bijzonder het maken van de fenestratie, heeft enkele risico's. Net onder de voetplaat ligt namelijk het vestibulum, een onderdeel van het evenwichtsorgaan. De vloeistof in het vestibulum, de perilymfe, staat in direct contact met de vloeistoffen van de cochlea. Schade aan deze binnenoorstructuren kan leiden tot draaiduizeligheid, tinnitus en gehoorverlies.

Traditioneel werd de fenestratie in de voetplaat gemaakt met een scherp micro-instrument of een microboor. Voor deze methode is er behoorlijke mechanische energie nodig. Deze krachten kunnen schade berokkenen aan de delicate binnenoorstructuren. Een methode zonder direct contact, bijvoorbeeld door gebruik te maken van een laser, lijkt in eerste instantie beter. Echter, ook het gebruik van een laser brengt risico's met zich mee. Er kan warmte optreden, maar er kunnen ook mechanische en akoestische effecten optreden.

Het doel van dit proefschrift is om de verschillende effecten, die ontstaan door het gebruik van een laser bij stapedotomie, in kaart te brengen. Met deze kennis kan er een keus gemaakt worden welke laser het meest geschikt is om te gebruiken voor stapedotomie.

Literatuuronderzoek

In **hoofdstuk 2 en 3** wordt het beschikbare bewijs in de literatuur, over resultaten van stapedotomie met de laser, systematisch beschreven. In **hoofdstuk 2** worden de gehoorsresultaten beschreven voor de conventionele techniek, vergeleken met de techniek met de laser. In **hoofdstuk 3** wordt er gekeken naar verschillen in resultaat bij het gebruik van verschillende lasers. In Pubmed, Embase, Cochrane Library, CINAHL en Scopus; werd gezocht naar beschikbaar bewijs. De toepasbaarheid en de kwaliteit van de studies werden beoordeeld. Een studie werd niet meegenomen in de uiteindelijke analyse, als deze slecht toepasbaar was of in opzet van lage kwaliteit. Twee auteurs hebben, onafhankelijk van elkaar, de kwaliteit van de studies beoordeeld en de data geëxtraheerd.

In **hoofdstuk 2** worden de resultaten getoond van de vergelijking tussen de conventionele en de laser techniek. Met de zoekstrategie werden 21 artikelen geïdentificeerd. Dertien artikelen vielen af, door de slechte kwaliteit van de opzet van de studies. In deze studies viel op dat de standaardisatie van de behandeling ontbrak of er veel patiënten uitvielen in de follow-up. Acht studies werden geïncludeerd voor de analyse, allen met een matige kwaliteit. De studies toonden geen verschil tussen de groepen in ABG sluiting of percentage patiënten met vertigo. Echter, zowel breuken in de voetplaat, als het ontstaan van perceptieve slechthorendheid, was meer voorkomend in de conventioneel behandelde groep. Om het risico op deze nadelige effecten te verminderen, is het gebruik van de laser aan te raden.

In **hoofdstuk 3** wordt het verschil in uitkomst, tussen verschillende lasers onderling, vergeleken. Er werden 8 studies gevonden die de gehoorresultaten tussen twee lasers vergelijken. Zes studies werden geëxcludeerd in verband met een slechte studieopzet of een slechte toepasbaarheid. Een veel voorkomende beperking in de studies was een ontbrekende standaardisatie van de uitkomstmaat. Uiteindelijk konden twee studies geïncludeerd worden voor de analyse. Vincent e.a. vergeleek in een - niet gerandomiseerde - serie de CO_2 en KTP laser.[1] Hij vond een minimale betere ABG sluiting bij de CO_2 laser, maar dit verschil lijkt klinisch weinig relevant. Marchese e.a. vergeleek de Er-YAG en CO_2 laser en vond duidelijk betere ABG sluiting bij de CO_2 laser.[2]
Er is helaas niet meer bewijs beschikbaar over het verschil in uitkomsten tussen lasers. Uit het huidige bewijs kunnen geen definitieve conclusies worden getrokken, over welke laser men het best kan gebruiken voor het maken van de fenestratie bij stapedotomie.

Binnenoormodel

In **hoofdstuk 4, 5 en 6** maken we gebruik van een binnenoormodel en high speed opnames, om de effecten die optreden rondom de voetplaat bij stapedotomie met de laser, in kaart te brengen. Dit binnenoormodel bestaat uit een reepje gel, waarin een vestibulum is gemaakt. Dit vestibulum werd gevuld met fysiologisch zout en bovenop werd een humane, ingevroren stapes geplaatst.
Effecten die optreden tijdens het maken van een fenestratie met de laser, kunnen worden voorspeld afhankelijk van het absorptiepatroon van de lasergolflengte in water. De verwachting is dat lasergolflengtes met een hoge absorptie in water (en dus ook in de perilymfe) meer opwarming zouden moeten laten zien, dan lasergolflengtes met weinig absorptie in water. De 10,6 µm golflengte van de CO_2 laser wordt sterk geabsorbeerd in water. Direct wanneer het de perilymfe bereikt, zal het worden geabsorbeerd en daardoor hitte veroorzaken. De 532 nm KTP laser, daarentegen, wordt nauwelijks

geabsorbeerd in water. Het laserlicht zal penetreren door de perilymfe, tot het de randen van het vestibulum bereikt. Hier bevinden zich de kwetsbare neuro-epitheliale cellen, die sterk gevasculariseerd zijn. In deze gepigmenteerde gebieden zal de KTP laser worden geabsorbeerd en mogelijk schade aanrichten. De golflengtes van de Thulium en Diode laser, respectievelijk 2 µm en 980 nm, zullen gedeeltelijk worden geabsorbeerd in de perilymfe.

Om de warmte effecten in kaart te brengen, werd gebruik gemaakt van de Schlieren opname techniek.[3] Bij deze techniek worden onregelmatigheden in de brekingsindex van een transparant medium in kaart gebracht. Deze onregelmatigheden worden in dit geval veroorzaakt door warmte. Licht dat passeert door het water, zal worden afgebogen door de warmte, die door de laser is ontstaan. Het afgebogen licht gaat door een regenboogfilter, waardoor er uiteindelijk verschillende kleuren ontstaan in de opname. De opnames geven een gekleurde warmteontwikkeling weer, waarbij de dynamiek van de warmteontwikkeling in kaart wordt gebracht. Met een sterke lichtbron, kunnen opnames tot 500 beelden per seconden worden verkregen. Deze techniek geeft relatieve temperatuursveranderingen weer. Het geeft echter geen absolute temperatuursveranderingen weer.
In **hoofdstuk 4 en 6** worden de resultaten van de high speed Schlieren opnames van de KTP, Diode, Thulium en CO_2 laser getoond. Na een eenmalige pulse met de KTP of Diode laser op een intacte voetplaat, werd er geen warmteontwikkeling gezien in het vestibulum. Na fenestratie met de CO_2 laser, zagen we dat de energie zeer snel werd geabsorbeerd, waarbij er kleine vaporisatie belletjes ontstonden (hetgeen temperaturen van > 100 °C aantoont). Het hittepatroon bleef gelokaliseerd direct onder de voetplaat en koelde weer snel af. Met de Thulium laser werden er uitgebreidere verwarmingseffecten gezien, tot 1 mm onder de voetplaat. In het hittepatroon werden meerdere gekleurde ringen gezien, dit duidt op een sterke opwarming.

Naast opwarming kunnen er ook mechanische effecten optreden in het vestibulum tijdens fenestratie van de voetplaat met de laser. Met snelle absorptie in de perilymfe, kunnen vaporisatie bellen ontstaan. Wanneer deze bellen imploderen, kunnen drukgolven ontstaan. Tijdens ablatie van het bot kunnen daarnaast ook akoestische effecten optreden. Deze mechanische en akoestische effecten kunnen schadelijk zijn voor de binnenoorstructuren.
De bovengenoemde effecten treden op in een zeer korte tijdsspanne en zijn met het blote oog niet waar te nemen. Om ze beter te kunnen bestuderen, maakten we high speed opnames, tot 4000 beelden per seconde. Door deze beelden in vertraging af te spelen,

wordt er duidelijk wat er tijdens de 100 ms van de pulse gebeurd in het vestibulum. In deze opzet werd ook simultaan het geluid opgenomen, door een ingebouwde hydrofoon. In **hoofdstuk 5 en 6** worden de resultaten van de mechanische en akoestische effecten getoond voor de vier lasers. De KTP en Diode laser gaven minimale mechanische en akoestische effecten. Bij de CO_2 laser ontstonden er minuscule belletjes in het vestibulum. De implosies van deze belletjes werden teruggezien in de akoestische metingen. Bij gebruik van de Thulium laser, worden er veel grotere bellen gezien in het vestibulum. De Thulium laser genereerde daarnaast het meeste geluid. Het dient echter gezegd te worden, dat alle lasers significant minder geluid maakten, dan het geluid van een conventionele microboor.

Diermodel

In theorie verwacht men niet dat de KTP laser veel mechanische of verwarmingseffecten zal laten zien in het vestibulum. De 532 nm golflengte wordt immers nauwelijks geabsorbeerd in de perilymfe. Het gevaar bij deze laser zit hem in het feit dat deze laser het vestibulum zal penetreren, totdat de wanden van het vestibulum worden bereikt. Ter plaatse van de sterk gevasculariseerde neuro-epitheliale cellen, die hier gelegen zijn, zal het laser licht worden geabsorbeerd. Potentieel kan deze directe straling direct schadelijk zijn voor deze zintuigelijke cellen.
In **hoofdstuk 7** worden de resultaten getoond van een *pilot* project in 6 cavia's. De cochlea van de cavia is eenvoudig bereikbaar, door het openen van de bulla achter het oor. The dikte van het bot van de cochlea is vergelijkbaar met de dikte van de humane stapes. De afstand tot aan het basilair membraan is bij de cavia ongeveer 3 mm, hetgeen overeenkomt met de diepte van een humaan vestibulum.
In deze studie werd er een cochleostomie uitgevoerd met de KTP-laser, hiermee werden 4 perforaties gemaakt. De normale klinische instellingen werden gebruikt (1 W, 100 ms), maar ook hogere instellingen tot 5 W in 100 ms. In de histologische preparaten zagen we geen afwijkingen aan het orgaan van Corti of het basilair membraan met de lichtmicroscoop. We zagen wel uitgebreide bloedstolsels in de vaten in de wand van de cochlea en substantieel vrij bloed in de scala tympani.

Om de vraag te beatwoorden, of de bovengenoemde effecten, schade zouden kunnen berokkenen aan de functie van het binnenoor, werd er een vergelijking gemaakt tussen de lasers. Er werden akoestisch opgewekte CAP gemeten bij de cavia, na het verrichten van een cochleostomie met de lasers. Resultaten van deze studie worden weergegeven in **hoofdstuk 8**. Er werd een afname gezien in CAP amplitudes en verhoging van de CAP drempels na cochleostomie bij alle lasers. De toename in de drempels was significant groter in de hogere frequenties. De Thulium laser liet de grootste verschuiving van de drempels zien, KTP de kleinste. De Diode en CO_2 laser zaten hier tussenin. De drempelverschuivingen waren klein voor de verschillende frequenties, maar bij 16 kHz was er een duidelijk zichtbare en significante verslechtering voor CO_2 en Thulium laser. Er dient wel gezegd te worden dat onze laatste meting plaatsvond 4 uur na de cochleostomie met de laser. Het is mogelijk dat deze drempelverschuivingen deels tijdelijk van aard zijn en nog herstellen na langere tijd. Herstel kan optreden in weken, zeker als de drempelverschuiving klein is. Eerder onderzoek toonde aan dat verschuivingen van meer dan 15 dB (als gezien bij de CO_2 en Thulium laser in ons experiment) permanent zijn.[4]

Patiëntenserie

In **hoofdstuk 9** worden de resultaten getoond van een niet gerandomiseerde vergelijking tussen de Thulium en CO_2 laser in primaire stapedotomy voor otosclerose. We vergeleken 98 operaties uitgevoerd met de Thulium laser, met 96 ingrepen met de CO_2 laser. Groepskarakteristieken waren vergelijkbaar, alle patiënten werden geopereerd door dezelfde operateur met dezelfde techniek. De postoperatieve controle bestond uit het verrichten van een toonaudiogram op 3 en 12 maanden.

Er werd een significant hoger succespercentage gezien bij patiënten behandeld met de CO_2 laser, vergeleken met de Thulium groep. Succes werd gedefinieerd als een ABG sluiting binnen 10 dB. Bij de Thulium groep werd een gemiddelde achteruitgang gezien in de beengeleiding van 1,6 dB (SD 6,9), in tegenstelling tot de 1,4 dB (SD 4,0) verbetering in de CO_2 groep. De vraag is hoe klinisch relevant deze verschillen zijn. Zorgwekkender was het feit dat er 4 patiënten waren in de Thulium groep met SNHL (4,4%) en 3 patiënten met tinnitus (3,1%). Deze nadelige effecten werden niet gezien in de CO_2 laser groep.

Conclusie

In dit proefschrift werd een gedetailleerd overzicht gegeven over de effecten die optreden tijdens stapedotomie met de laser. Thulium laat slechtere resultaten zien, vergeleken met de KTP, Diode en CO_2 laser, in experimenten van zowel het middenoormodel als het diermodel. Bijkomend, in de patiëntenserie zien we een hoger percentage patiënten met substantiële SNHL en tinnitus, vergeleken met de CO_2 laser. Het is dan ook af te raden deze laser: de Thulium laser te gebruiken bij stapedotomie. De KTP, Diode en CO_2 lasers, lijken veilig voor het gebruik bij stapedotomie.

Voor de chirurg

Bent u geïnspireerd geraakt om een laser te gaan gebruiken bij stapedotomie, kijk dan nog eens goed naar onze '*tips for the surgeon*' in de appendix.

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1. Vincent R, Bittermann AJ, Oates J et al. KTP versus CO_2 laser fiber stapedotomy for primary otosclerosis: results of a new comparative series with the otology-neurotology database. Otol Neurotol 2012;33:928-933.

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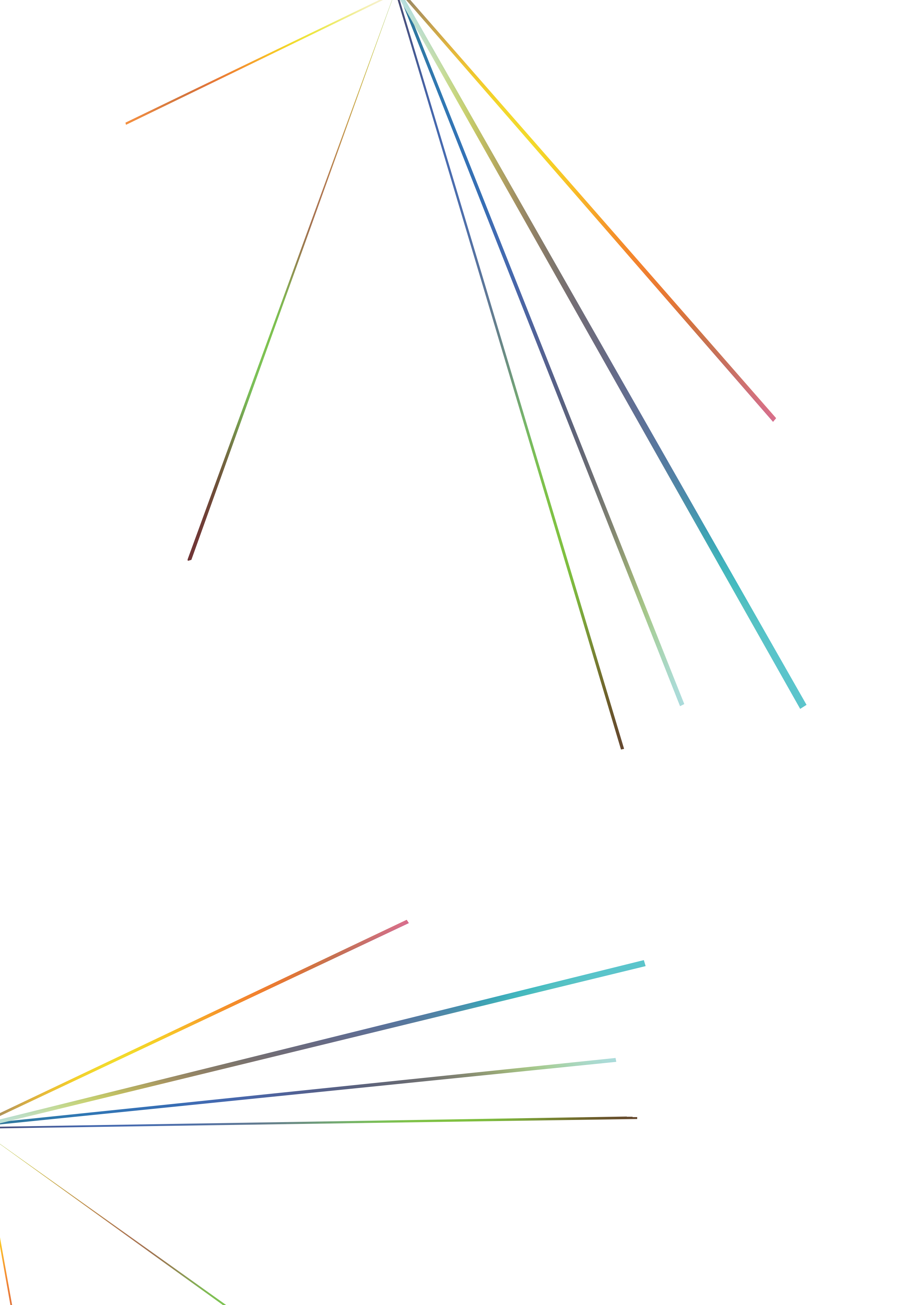

Appendix
Dankwoord
List of publications
List of abbreviations
Curriculum vitae

Appendix

The person operating the laser is primarily responsible for its safe use. To avoid hazardous situations, it is important that the surgeon has enough knowledge of the laser and its possible dangerous effects. Precautions should be taken, to ensure safety of the patient and of all personnel in the operating theatre. A few tips to get you started:

Get educated!

When starting to work with a laser, make sure you get the right training. How does the laser work? What are its potential hazardous effects? Many hospitals have specialized training programs for laser-using personnel on laser safety issues. Get acquainted to your local laser-safety officer. They often work for the hospital's Medical Technology Department. Read the information provided by the laser-producing company carefully.

Prepare the operating theatre

Medical used lasers are typically Class IV lasers. Eye or skin damage is likely to occur when exposed to a direct or reflected beam. Exposure to scattered or diffused light can also be hazardous. Therefore, the surgery should be performed in a "laser controlled area". All glass windows should be covered and warning signs should be placed at all entries. Minimization of reflecting surfaces is highly advised, as they might scatter the laser light. Make sure there is a fire extinguisher available.

Patient safety

In case of general anesthesia, close and cover the patients' eyes. When applying local anesthesia, provide safety goggles to the patient. Disinfect with liquids on a non-alcohol basis to minimize fire hazard. Make sure the disinfectant has dried before starting using the laser.

Personnel safety

Work with trained personnel. Unnecessary personnel should wait outside and re-enter the operating theatre when the laser is no longer needed. The most important danger of the laser light is damage to the eyes. All personnel should wear appropriate protective eyewear. Be aware: not every safety goggle prevents every laser wavelength from passing. Make sure the goggles block the appropriate wavelength. As the surgeon, you can either wear a goggle or use a filter in the microscope instead.

Laser use

Your laser is now ready for use. After switching it on, it is on standby mode. Check the laser settings (CW versus pulses, pulse time, energy per pulse). Use the lowest possible settings, thereby ensuring minimal side effects to the patient. Pre-carbonise the laser tip if necessary. When you are ready, make small perforations in the footplate. Choose correct placement of the laser fiber before hitting the footswitch. Take your time in between the different laser shots, to minimise accumulation of heat. When you are not using the laser, ask someone else to put it again on a standby mode.

Keep it safe

To maintain laser safety in the long run, make sure there is a correct maintenance plan for the laser. Keep your team trained, for instance by following fresh-up courses on laser safety with the entire surgical team.

Dankwoord

"If we knew what it was we were doing, it would not be called research, would it?" - Albert Einstein

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En nu...?

.... y ahora.... tengo tiempo para aprender español....

Curriculum Vitae

Digna Maria Anne Kamalski was born on April 20th 1981, an Easter Monday, in Geldrop, the Netherlands. In 1999 she finished her gymnasium cum laude at the Bisschoppelijk College in Weert. Subsequently she started her medical study at the University Utrecht. In 2002 she followed an internship Gynaecology and Obstetrics in the *'s Lands Hospital*, Paramaribo, Suriname.

After finishing her studies in 2005, she began working at the Emergency Department at the Hofpoort Ziekenhuis in Woerden. The next year she was given the opportunity to do research at the Gadjah Mada University in Yogyakarta, Java, Indonesia. Under supervision of prof. dr. I. B. Tan, she conducted research in the field of nasopharyngeal cancer. Her research project suddenly ended on May 27th 2006, when an earthquake struck Yogyakarta. She spent her remaining time working for a local aid organization "*Rumah Teman*".

In 2007 she started at the Otorhinolaryngology and Head & Neck Surgery Department at the UMC Utrecht, where she did her residency from 2008 until 2013. In 2009, with the arrival of prof. dr. W. Grolman to the department, she started her research on effects of lasers in stapedotomy. This project was done in collaboration with prof. R.M. Verdaasdonk and resulted in this thesis.

Currently she is working as an otorhinolaryngologist at the UMC Utrecht. Also, she is the coordinator of the Master Language and Speech Therapy Science at the University of Utrecht.

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List of abbreviations

ABG	Air Bone Gap
AC	Air Conduction
BC	Bone Conduction
CAP	Compound Action Potential
CO_2	Carbon Dioxide
CW	Continuous Wave
dB	Decibel
dB (A)	Decibel, in A weighting
dB SPL	Decibel, sound pressure level
Er-YAG	Erbium-Yttrium Aluminium Garnet
Hz	Hertz
IR	Infrared
kHz	Kilohertz
KTP	Potassium (*Kalium)* Titanyl Phosphate
NaCl	Natrium Chloride
ORL	Otorhinolaryngology
PTA	Pure Tone Audiometry
RCT	Randomized Controlled Trial
SD	Standard Deviation
s.e.m.	Standard error of mean
SNHL	Sensorineural Hearing Loss
SP	Super Pulse

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