Tjeerd de Boorder

New near infrared fiber delivered laser sources for surgery:

physical aspects and clinical implementation

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New near infrared fiber delivered laser sources for surgery:
physical aspects and clinical implementation

Nieuwe fiber geleide lasers in het nabij infrarood:
fysische aspecten en klinische implementatie

(met een samenvatting in het Nederlands)

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1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Thermal techniques in surgery

Surgery and blood loss

Surgical treatments date back to the prehistoric era. Ever since, infections and bleeding have been the major complications. Different techniques have been developed through history to reduce blood loss, especially sutures, staplers or glue[1]. Thermal energy has also been introduced to control bleeding of the surgical plane. In the early days of surgery (medieval times) hot charcoal or heated iron was used for coagulation purposes[1,2]. For the last few decades, electric currents are used for heating of tissue and thereby achieving haemostasis. More recently, light (photons) produced by lasers (Light Amplification by Stimulated Emission of Radiation) is converted into heat when it is absorbed in the tissues which enables coagulation of (micro)blood vessels and ceases the bleeding[3]. In current medicine, a combination of mechanical and sophisticated thermal techniques is usually applied for stopping and preventing blood loss during surgery.

Thermal techniques to treat tumors

The destructive effect of thermal techniques on tissue gradually prompted applications to treat tumors as an alternative for resection by scalpel. Many thermal modalities are nowadays available on the market and different physical principals are used (Table 1).

Electrosurgery is one of the most common instruments in the operating theatre (OR)[5,6]. Every OR has an electrosurgical generator and this equipment has developed into a precise surgical instrument with many applications. Also many kinds of instruments for applying electrosurgery to the patient for cutting, coagulation or vaporization have been developed[7]. The most common electrosurgical modality is monopolar electrosurgery[5]. The surgeon activates an electrode from a handpiece (electrode), with a small contact surface, creating a high-power density resulting in a high temperature due to the tissue impedance. The high temperature enables tissue coagulation, cutting, or ablation[5,6]. The patient itself is part of the electric circuit, and the current is returned by a negative electrode (also called return-electrode) with a large surface attached to the patients skin, large enough not to create thermal damage by electrical current[4]. The electrical currents are generated in a high frequency (100kHz), which does not interfere with nerve stimulation and the electrical current runs through the path of least resistance[4]. Monopolar electrosurgery can also be applied via laparoscopic instruments[5,6].
The current follows the path of least resistance and has therefore a preference for

blood vessels and ducts which can be an advantage for achieve haemostasis. However, it can also result in extensive damage to the vasculature delaying the healing response.

A disadvantage of electrosurgery is that the patient is part of the electric current. Due to alternative electric pathways, poorly insulated instruments or capacitive coupling, thermal effect can occur at unnoticed far outside the area of surgery[8,9]. Another disadvantage of electrosurgery is the contraction of muscle tissue while applying electrosurgery directly on muscle. This can be unwanted during surgery on muscle tissue, e.g. when excising a tumor from the tongue[10].

In bipolar electrosurgery, the current flows between two electrodes close to each other e.g. between the tips of the legs of forceps which is often used for micro surgery[5,6]. Also, bigger forceps or graspers are used to coagulate or seal thicker tissue parts as the greater omentum during bowel surgery. Before these bigger bipolar graspers were invented, the greater omentum had to be ligated with separate resolvable ligatures, which is more time consuming compared to a bipolar grasper[11].

Besides electrosurgery other energy devices are used to create thermal effects based on various other physical principles (Table 1[4,12–16])

Surgical lasers

Laser (Light Amplification by Stimulated Emission of Radiation) is a unique light source by emitting a small parallel beam of intense mono-chromomatic (one specific wavelength/color) light: (A) This enables a high intensity at a small surface area inducing high temperature by absorption of light at the surface. (B) The specific color/wavelengths of lasers can target particular chromophores within tissue like blood and melanin and tissue penetration ranges from one μm up to several mm. (C) The small parallel beam enables transport through thin optical fibers (typically 100-600μm) with minimal loss and thus, many locations within the human body can be reached.

Surgical lasers are already used for many different applications[3]. Lasers are used in surgery for the similar purposes as electrosurgery. However, the specific wavelength determines laser-tissue interaction[17]. As some wavelengths penetrate deeply in the tissue, others have a superficial effect. When choosing a laser for surgical purposes it is important to realize to which extent the light will penetrate into the tissue. To understand the influence of the laser wavelengths on tissue, it is important to comprehend the principles of light interaction with tissue.

TABLE 1. Overview of common energy delivery devices for surgical applications

Energy delivery device	Mechanism
Electrosurgery	Electrical current running through the body and creating heat on the applied spot.
Radio Frequent Ablation	Bipolar electrode (needle). High frequency (400kHz) electric current creating a controlled ablated zone, by local tissue heating
Ultrasonic	Vibrations at frequencies between 23.5 and 55.5kHz and high vibrational amplitude (between 80 and 360μm) to disrupt tissue.
HIFU (High-intensity Focussed Ultrasound)	An acoustic lens is used for focusing ultrasound waves to enable temperature rise in tissue.
Plasma(Argon)	An intermediate ionized gas (medium for example Argon gas) is directed to the tissue used and excited to transfer energy.
Microwave	Electromagnetic waves in the frequency between 915MHz and 2.4GHz create harmonic oscillations in water as the dipoles align themselves in the alternating electric field, creating heat.
Waterjet	Disruption and hydrodissection of tissue caused by a high pressure (30-70bar) water jet stream.
Electroporation	High-voltage sub-millisecond electrical pulses to induce cell death via disruption of the membrane lipid bilayer.
LASER (Light Amplification by Stimulated Emission of Radiation)	Monocromatic, coherent bundle of photons able to absorb in tissue and creating heat.

As light comes in contact with tissue the following events occur[3,4,17]. (Figure 1).

- Absorption: The part of the laser light that is transformed into heat.
- Reflection: The part of the light that is reflected from the surface.
- Scattering: The part of the light that is randomly reflected in the tissues into different directions.
- Transmission: The part of the light that is transmitted through the tissue.

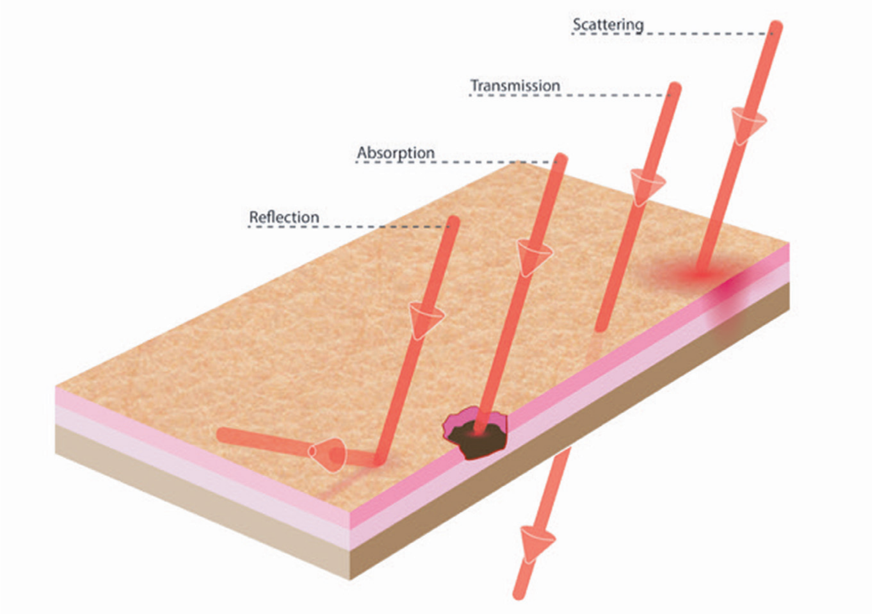

FIGURE 1. Laser tissue interaction, scattering, transmission, absorption and reflection.

If a surgeon chooses a laser system to perform a precise excision of soft tissue without damaging underlying structures it is important to choose a wavelength that has a high rate of absorption superficially of the surgical plane and a relative short pulse time to prevent heat conduction into the depth of the tissue. A wavelength has to be chosen that has a high absorption coefficient that is present in all kinds of tissue in order to be independent of specific chormophores such as melanin. As water is the most prominent component of the body, it is logical to choose a laser emitting light with a wavelenght having a high energy absorption in water.

Surgical lasers in the near and middle infrared spectrum
Figure 2 shows a range of commercially available lasers in de near infrared and the mid infrared spectrum. The graph of the absorption coefficient of water shows multiple peaks with corresponding laser systems. When evaluating the laser systems from right to left, the CO_2 laser wavelength (10.600nm) has a high absorption in water. The CO_2 laser is appreciated for many applications in surgery, and the laser beam is delivered through vulnerable articulated arms and not by a flexible silica laser fiber[18]. Hollow wave guide fibers became available but it is not possible to use this device in an aqueous environment.
At 3000nm, a peak in the water absorption coefficient appears. The Er:YAG laser operates at 2940nm. The absorption in water is so high, that the coagulation effect is

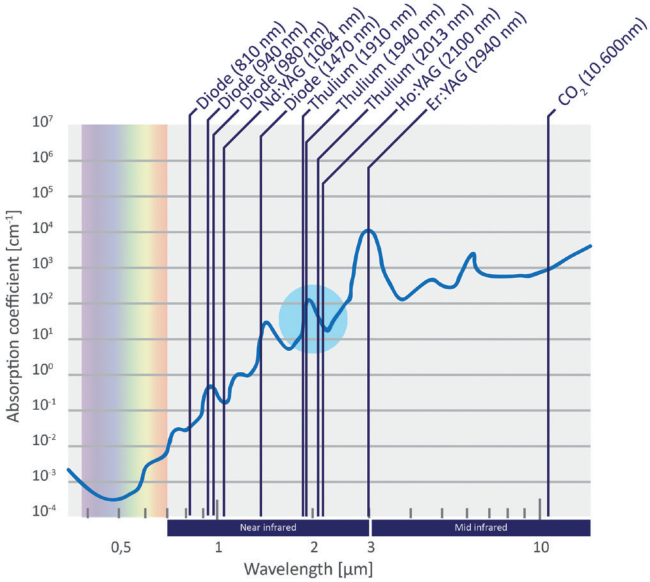

FIGURE 2. Commercial available lasers in relation to the absorption coefficient of water in the infrared region.

too low to enable sufficient haemostasis. Also this wavelength is problematic for fiber delivery[19].

The next peak in the water absorption spectrum is around 2000nm. In the last two decades this wavelength has been available into commercial laser systems and can be delivered through low OH silica fibers. It is a relatively new type of laser and a variation of surgical specialties have used this wavelength for clinical applications[20–22]. Compared to the other wavelengths mentioned in the last paragraphs, the 2000nm peak is between the lower and the highest region of water absorption in the infrared spectrum. Several laser clinical laser systems exist. The Ho:YAG laser was first introduced around 1990 and is a pulsed laser, with strong mechanical effects. The Thulium laser was clinically introduced around 2005 and is a continuous wave (CW) laser. Theoretically, this wavelength would cut effectively through soft tissue with additional coagulation. In addition, the ability to deliver the 2000nm wavelength though silica fibers make it suitable for endoscopic surgery, as laser fibers fit through nearly every working channel of endoscopic instruments. The Thulium laser has been commercially available since 2005. There is a slight difference in wavelength of the clinical systems. Typical Thulium lasers have a wavelength between 1940nm and 2013 nm.

The clinical difference between these wavelengths has not been demonstrated until now.

At the 1470nm region another high water absorption peak is present and a diode laser with fiber delivery is available[23]. Moving further to the left of the of the slope of the water absorption coefficient the value decreases rapidly. This is still in the infrared region and typical laser wavelengths for clinical use are the 810nm, 940nm, 980nm (diode lasers) and the 1064nm Neodymium:Ytrium Aluminium Garnet laser (Nd:YAG), which all have similar water absorption en relative comparable tissue effects[17].

The 810nm, the 940nm, the 980nm and the 1064nm Nd:YAG laser have deep light/ energy penetration in tissue compared to the other infrared laser discussed above with high energy absorption in water. However, a carbonized fiber tip (on the 810, 940, 980 and the 1064nm lasers) transforms the laser-tissue effect of a laser with high water absorption, i.e. the light is absorbed in the carbon layer, resulting in a "hot" fiber tip (figure 3). This property should be carefully considered when using the 810-1064nm lasers. When superficial ablation is needed a carbonized tip is absolutely necessary.

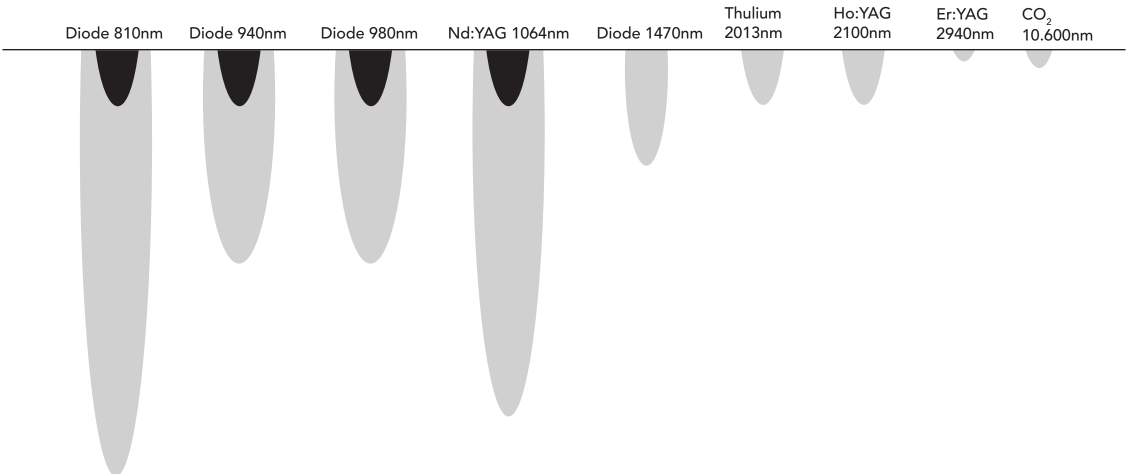

FIGURE 3. Showing the relative light penetration of infrared lasers tissue. The four lasers form the left have deep light penetration with a clean fiber tip (gray surface). With a carbonized fiber tip the laser light is mainly absorbed in the carbon, resulting in less light penetration in the tissue (black surface). The five lasers from the right have a more superficial light penetration as a result from good absorption of laser light in water.

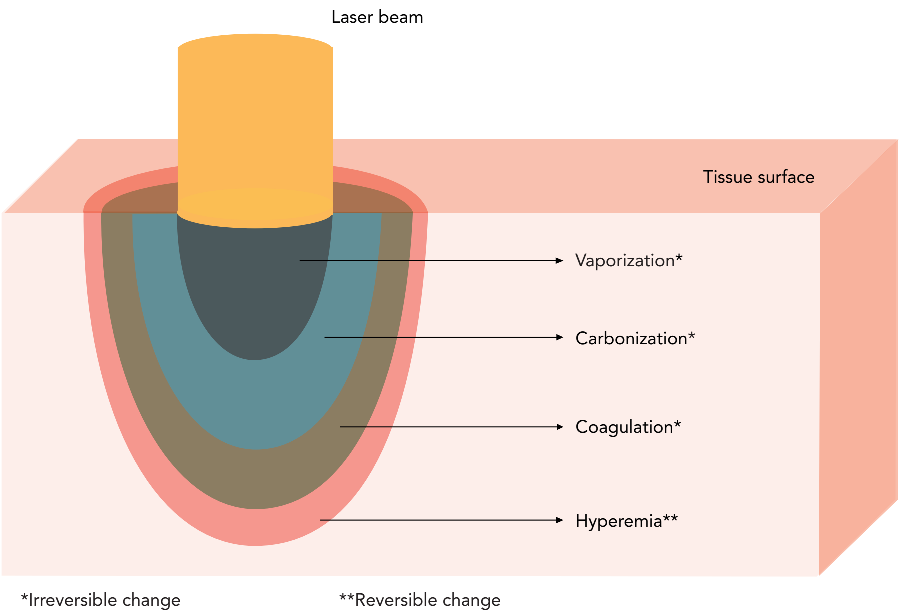

FIGURE 4. Thermal zones in soft tissue and subsequent thermal damage.

A clean non carbonised fiber tip (810nm, 940nm,980nm,and 1064nm) will cause thermal damage in deeper layers of tissue which could be unwanted.[24,25]

Thermal damage zones in soft tissue

Figure 4 shows the different thermal/damage zones in soft tissue caused by laser light absorption. Depending how the thermal energy is generated, different tissue regarding width and depth of the thermal/damage zones can be observed. If a narrow thermal damage zone is preferred, a laser with high local absorption (for example a laser with high energy absorption in water) is needed, like the Thulium laser.

Thermal effects in tissue

Arrhenius

Different parameters are of interest when heating human tissue for surgical purposes. Tissue is not homogenous and the different structure of layers and composition makes tissue react with variable reaction to applied heat[29]. The major component of tissue is water (> 60% [30]). As water is the major component it dominates the thermal properties (specific heat $J \cdot kg^{-1} \cdot K^{-1}$).

For obtaining the right thermal effect, it is important to understand the thermal dynamic properties of the treated tissue in relation with the chosen energy modality. Many energy delivery devices are available for clinical use and it is difficult to predict the tissue-effect of the different sorts of energy delivery devices. However, the Arrhenius formulation incorporates thermal dynamic properties and is useful in predicting and describing the effects in tissue heating[31].

The Arrhenius formulation was described by the Swedish scientist Svante Arrhenius in 1889. This equation predicts the point at which cells are irreversibly damaged when they are exposed for a certain time to a particular temperature. In this formulation, the multiple thermodynamically independent processes are calculated separately. The Arrhenius formulation can be used to compare the tissue effect of different energy sources i.e. the conversion of energy into heat and different kinds of tissue. Once the energy is converted into local tissue heating the thermodynamic principles remain the same for all energy delivery devices[4,31,32].

To understand the effect of heat on tissue it is important to realize that both time and power are important parameters. For example, if a certain amount of energy is concentrated in a very short period of time, the effect on tissue will be different than when the energy is exposed out in a longer period of time figure 5[3]. These power/ time related effects have been extensively studied. This knowledge is important when new energy delivery devices are developed. Extensive evaluation is needed for understanding the clinical possibilities and the risks of energy delivery devices for a safe clinical introduction. On the one hand the mathematical approach and on the other hand *in vitro, animal* and *in vivo* experiments are essential tools to predict thermal effects in a clinical situation. In some cases it is possible to reduce animal testing by smartly developing visualizations for *in vitro* experiments.

For understanding of the effect of heat on tissue the following events occur if certain temperatures are reached[3,4,17].

- At 50°C for sufficient time, irreversible damage occurs to soft tissue
- Between 60 to 80°C, collagen denatures and the intramolecular hydrogen bonds of protein are broken. Elastin networks do not denature. As a result, soft tissue structures will shrink up to approximately one third of their initial length.
- Between 70 - 100°C tissue dehydrates and the water content decreases depending on the time of further temperature increase.

- Around 100°C water turns from liquid to vapour phase expanding 1600 times in volume. Since water is usually encapsulated in cell or tissue structures, the pressure and temperature can built up to 130°C and sudden conversion of cell water into steam leads to cell membranes rupture and steam escapes. The vaporization of tissue water around 100°C consumes more that 2x the energy to heat it to 100°C. It can take some time before all tissue water is vaporized.

Only 20-30 % of the tissue is left after all the water is vaporized and less energy is needed to heat up the tissue remains quickly to 250-300°C where the structure disintegrates and gases escape in fumes/smoke and tissue carbonizes. These important (non-linear) phases during tissue heating are shown in figure 6.

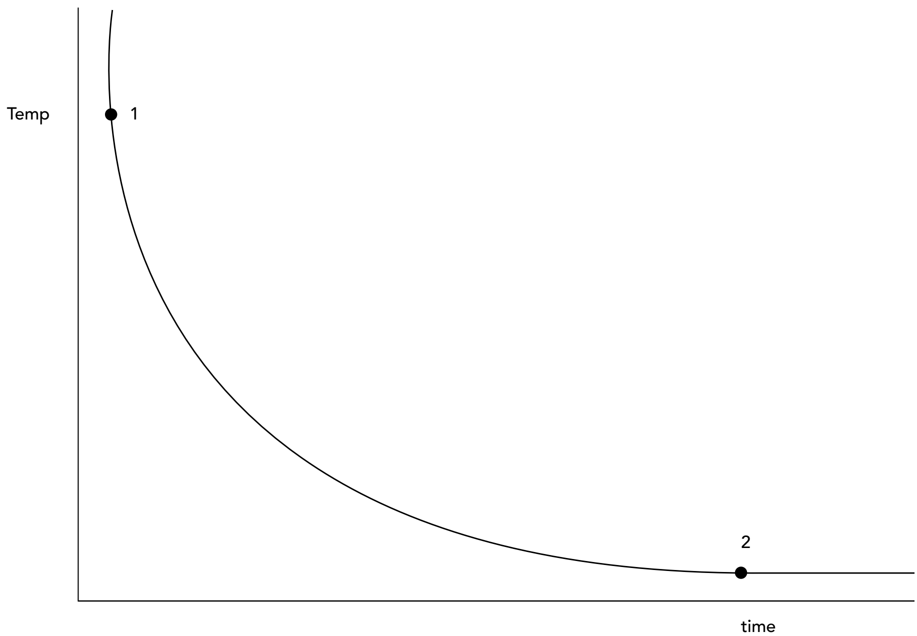

FIGURE 5. Tissue damage based on the Arrhenius equation. At point 1, a high temperature is exposed on tissue for a relative short period of time, resulting in much tissue damage. At point 2, the same amount of energy as in point 1 is used in a relatively long period of time, resulting in less tissue damage compared to point 1.

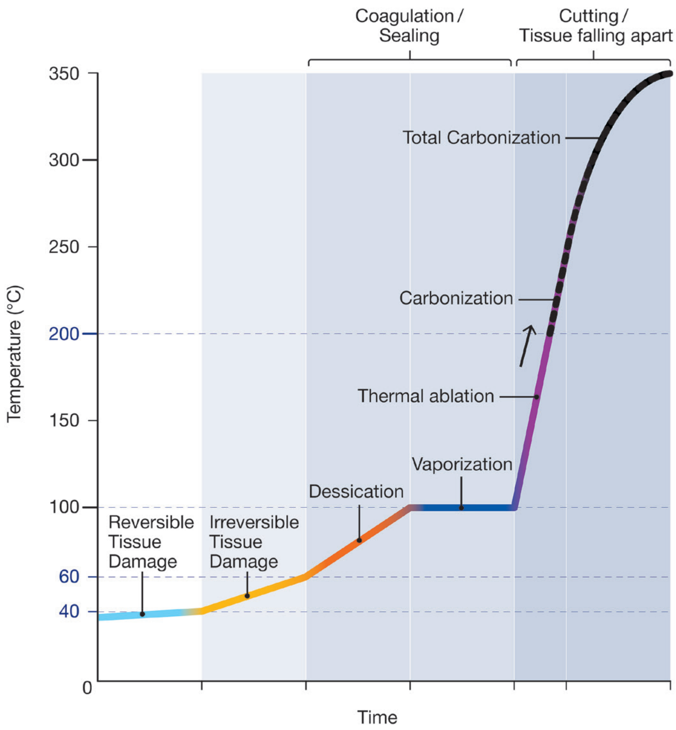

FIGURE 6. Relation between time and temperature on soft tissue. (with the courtesy of Olympus medical and Rudolf Verdaasdonk).

'Rule-of-thumb' model to predict tissue temperature/effects

In order to translate the physics in the paragraph mentioned above, a simple model can be used to understand the amount of energy needed to ablate a specific amount of tissue. The changes in tissue by temperature have been extensively studied with thermographic studies and the minimum energy that is necessary to ablate soft tissue can be calculated with the following assumptions.

- Energy losses due to conduction and convection is neglected when energy exposure time is below 0.01s.[26]
- Tissue contains 75% water
- No losses during energy transfer to the tissue
- Tissue solids are vaporized at 300°C

With the assumptions made above it was calculated that approximately 2J is necessary to ablate 1mm^3 of soft tissue[27,28]. Tissue temperature will reach temperatures above 100°C. All water is vaporized and temperature rises quickly which enables vaporization (figure 6). However, if the exposure time is >1s (instead of <0.01 s) and the other parameters are kept the same, more energy is needed to reach 100°C , due to dispersion of the energy in a larger volume by thermal conduction and tissue will not reach the ablation phase. This "rule-of- thumb" is independent of the energy delivery device as it is an energy distribution rule based on temperature exposure. This rule can be used to predict the tissue effect in relation to the amount of energy / exposure time/ type of tissue.

Aim and outline of this thesis

Energy delivery devices evolve and new devices are being developed continuously. Surgeons have to choose between many types of energy delivery devices based on different physical properties, which is challenging.

In this thesis, we focus on a relatively new energy device, the Thulium laser, which has been evaluated for *in vitro, ex vivo* and *in vivo* applications. The main objective is to evaluate the advantages and/or additional value of the Thulium laser in comparison to other (existing) energy devices in clinical applications especially in ENT and Neurosurgery.

Chapter 2 describes a review of the current surgical specialties and clinical applications for which the Thulium laser has been used.

Chapter 3 determines safe laser settings for Thulium laser-assisted endoscopic third ventriculostomy using an *in vitro* model, based on the color Schlieren technique. Also, two-year follow-up results are described in 106 patients.

Chapter 4 describes an *ex vivo* feasibility study of endoscopic intraductal Thulium laser ablation of the breast.

Chapter 5 describes the mechanical, thermal and acoustic effects with a 1470nm diode laser in stapedotomy.

Chapter 6 describes the mechanical, thermal and acoustic effects with a 980nm diode laser in stapedotomy.

Chapter 7 presents a novel handpiece for open laser surgery.

The Addendum describes a comparison of the Thulium laser and the Nd:YAG laser in the treatment of genital and urethral condylomata acuminata in male patients.

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HAVE WE SEEN THE LIGHT?

An overview of the medical applications of the Thulium laser

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Submitted

ABSTRACT

Objective

The Thulium laser is an infrared continuous wave laser with a wavelength around 2000nm with a high energy absorption in water. It is a relatively new continuous wave wavelength which is fiber delivered and has the highest energy absorption for a fiber delivered medical laser system. The Thulium laser could in some cases replace the CO_2 laser. There is an increasing interest by various surgical specialties. The objective of this study was to assess in which medical specialties and interventions the Thulium laser has been used since its introduction in 2005 and to assess clinical outcome in relation to other modalities.

Methods

A systematic bibliographic search was performed in Medline. All studies were categorized by specialty and type of intervention. Surgical interventions and the clinical results were described.

Results

216 studies were retrieved in 8 clinical specialties and 20 interventions/applications. Most experience has been gained in the field of urology followed by ear/nose/throat, dermatology and neurosurgery for cutting/coagulation in open and endoscopic procedures.

Conclusions

The Thulium laser has developed into a promising energy delivery device for a large variety of interventions. Most experience has been gained in urology. There is more potential for the Thulium laser in endoscopic procedures. The laser light is fiber delivered, and thus endoscopic working channels are very accessible for this type of energy delivery device. For open surgery applications, dedicated surgical tools need to be developed.

INTRODUCTION

The Thulium laser is relatively new in medicine. It has been clinically introduced around 2005 and the areas of application are increasing[1,2]. A unique property is that this laser combines cutting and coagulation and can be delivered through optical fibers[3]. The absorption coefficient of Thulium light in water is relatively high for a fiber delivery based laser. (fig 1.)

In contrast, to the other (pulsed) lasers in this wavelength region of the 2µm absorption peak of water, the Thulium laser light is emitted continuous wave. The wavelength of 2.0µm is in close to that of the pulsed Ho:YAG (Holmium:Yttrium-Aluminium-garnet) laser at 2.1µm. The Ho:YAG laser is considered as the working horse for urologists for lithotripsy procedures[4]. A typical Holmium laser delivers pulses between 300 and 600 µs at frequencies between 0.5 and 80Hz[5,6]. Due to the pulsed character cellular water is instantly heated over 100°C resulting in an explosive vapor bubble making fissures in surrounding tissue which seems less controlled compared to a continuous wave laser with similar wavelength as the Thulium laser[7,8]. A Thulium laser delivers light in a continuous laser beam or shutter controlled (seconds to milliseconds). Next to the common Thulium lasers operating at 2013nm, wavelengths of 1910nm, 1940nm and 2010nm are available. All these wavelengths are on the absorption peak of water[9,10] (fig. 1 and fig.2).

Thulium laser light can be generated either in a diode pumped crystal or long fiber doped with Thulium atoms acting as the laser cavity. Thulium fiber lasers have become available more recently. Fiber lasers are more compact and efficient with powers up to 100W. The wavelength can be tuned over hundreds of nm and millisecond pulses can be generated with peak powers up to 500W. The laser light generated within the thulium fiber is coupled into the 'normal' low OH silica laser fiber for delivery to the tissue[4,9]. Due to the high peak powers Thulium fiber lasers are considered as an alternative for Holmium laser lithotripsy[11].

The Thulium laser is used increasingly for clinical applications where electrosurgery is the gold standard due to combined cutting and coagulation effect delivered locally through small instruments without special precautions for adverse effects of electrical currents[12]. The Thulium laser light is efficiently absorbed in a 0.5mm superficial layer of tissue (water) heating the tissue above coagulation and water vaporization levels in a small area of a few mm depending on the laser parameters[2].

In this paper an overview is presented of the current acceptance of the Thulium laser in different medical specialties, the field of applications and clinical outcome in relation to other modalities.

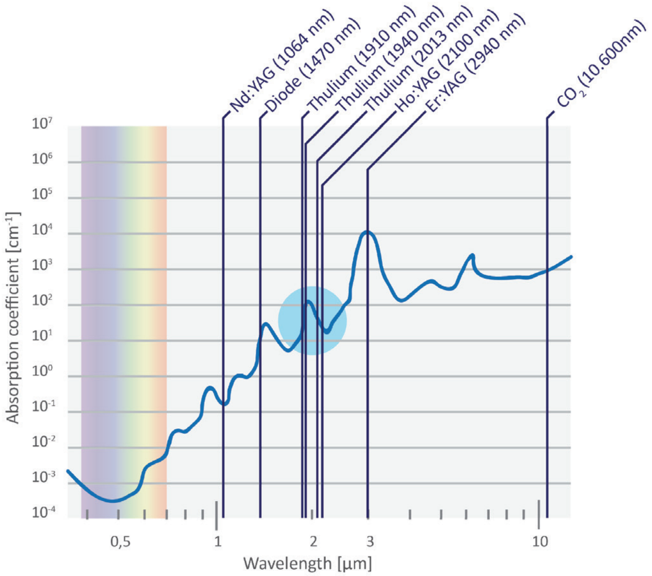

FIGURE 1. The absorption coefficient of water shows the difference in water absorption of typical commercially available laser systems. The Thulium laser around 2000nm is relatively new.

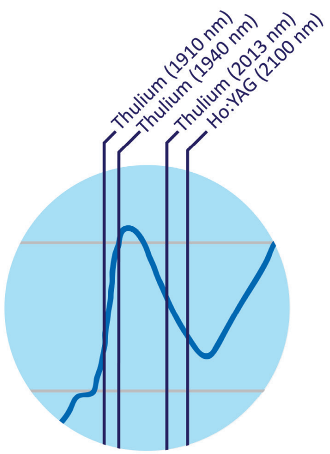

FIGURE 2. Enlarged part of an absorption peak of water from fig. 1, showing a variety of Thulium laser wavelengths and a Ho:YAG laser.

METHODS

Search strategy

A systematic bibliographic search was performed in Medline. The date of search was December 28th 2017. Thulium laser has several synonyms and these were combined (Table 1).

Since the Thulium laser already has a high acceptance rate in urology with its own acronyms the terms Thulep (Thulium Laser enucleation of the prostate), Thuvarp (Thulium laser vaporesection of the prostate), Thuvap (Thulium Vaporization of the prostate) and Thuvep (Thulium laser vapo-enucleation of the prostate) were also used. It is acknowledged that this gives a bias towards publications in Urology in this search. The retrieved studies were categorized according to medical specialty and type of intervention. Subsequently all surgical specialties which used the Thulium laser were described.

TABLE 1. Search for studies concerning the Thulium laser.

Database	
PubMed	Search
	(((((((((((((("thulium laser") OR "2 micron continuous wave laser") OR "2μ continuous wave laser") OR "2.0 micron continuous wave laser") OR "2-μ thulium laser") OR "Thulium fiber laser")) OR "TM:YAG")) OR "Thulep")) OR "Thuvarp")) OR "Thuvap")) OR "Thuvep".

RESULTS

From Medline 393 titles were retrieved. These titles were classified in different categories, shown in table 2 and figure 3. Studies in Chinese, Italian, German and Spanish, reviews and fundamental research were excluded, leaving 216 studies in different fields of medicine as shown in table 2. It was assumed that the most important studies have been published in English as the common language in the international scientific community.

Over the years, lasers at various wavelengths were introduced for surgical specialties. Firstly, the CO_2, Argon and the Neodymium: Yttrium aluminum garnet (Nd:YAG) laser where introduced in the 1970's[13,14] . Later these lasers were largely replaced by a variety of diode lasers and KTP (Potassium-titanyl phosphate) lasers. The Ho:YAG laser was first introduced around 1990 and the Thulium laser around 2005. Historically, urologists were interested in using lasers for prostatectomies. First reports for this application were published in the 1990'[15].

Following the applications in various clinical specialties will be discussed starting with the 'main user' Urology.

Urology

Prostate

The Thulium laser was mostly used (100 hits) for the treatment of benign prostate hyperplasia (BPH) including large studies (largest n=1080 patients)[16]. Typical laser parameters were a wavelength of 2013nm with a power between 70 and 200W continuous wave[17]. Different kind of Thulium laser techniques have been reported for treating BPH.[16] Bach et al. proposed nomenclature for prostate Thulium treatments[18]. ThuLep for blunt enucleation of the prostate, ThuVap for pure vaporization without producing prostate chips, ThuVarp for vaporesection of the median and lateral lobes of the prostate while keeping prostate parts small enough to enable rectoscopic evacuation[19] and ThuVEP for vapo-enucleation of the median and lateral lobes followed by morcellation inside the bladder.

Most studies prove that the Thulium laser is a safe and effective instrument in the treatment of BPH with low incidence of complications[20]. When using a laser for BPH instead of traditional transurethral resection, the use of saline is possible instead of nonelectrolyte fluid (typically 1.5% glycine solution) that can cause dilutionial hyponatremia[21], thereby reducing side effects including risk of haemorrhage in patients on oral anticoagulants[21–24].

TABLE 2. Number and percentage of studies found in Medline per specialty

Category	Number	Publications in time		
Period		2005-2010	2011-2017	Percentage
Urology				
Prostate	100	16	84	46
Lithotripsy	18	3	15	8.3
Bladder	14	1	13	6.5
Kidney	8	1	7	3.7
Urethra	5	1	4	2.3
Ureter	5	1	4	2.3
Penis	1	0	1	0.46
ENT	18	5	13	8.3
Dermatology	17	2	15	7.8
Neurosurgery	14	1	13	6.5
Gastro intestinal	6	2	4	2.8
Heart and Lungs	5	0	5	2.3
Gynaecology	4	1	3	1.9
Breast	1		1	0.46
Total	**216**	34	188	100

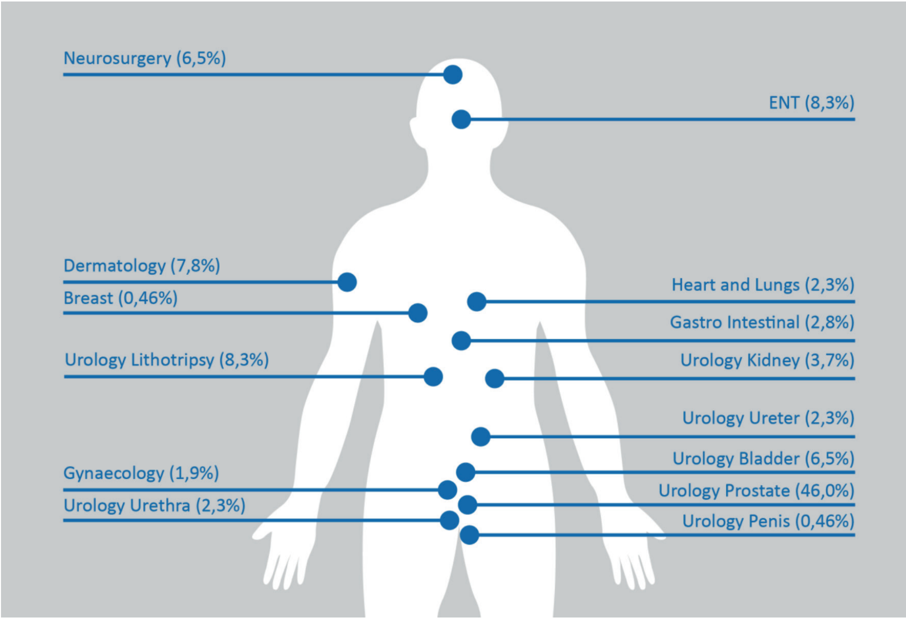

FIGURE 3. An overview of the specialties and the part of scientific papers.

Also the Ho:YAG laser and the KTP (Greenlight laser) were used for the treatment of BPH. Ho:YAG and Thulium laser seemed to be better in surgical efficacy and safety compared to diode lasers and KTP[25].

Lithotripsy

For fragmenting urinary stones (18 papers) a Thulium fiber laser has been used with a wavelength between 1908 and 1940nm[26–28]. The 1940nm wavelength nearly exactly matches the water absorption peak in the infrared spectrum[29] (fig1.). However, the most common lithotripter is a pulsed Ho:YAG laser with a wavelength at 2100nm. The studies described either *in vitro* or *ex vivo* experiments, but no clinical reports were published on this subject. The studies describing lithotripsy by Thulium fiber lasers were published by a single research group of Fried et.al.

Bladder

The Nd:YAG laser was introduced for bladder cancer in the 1970's but was abandoned shortly after that, probably caused by the long penetration depth in tissue that

accidentally resulted in bowel injury[30]. The Ho:YAG laser was introduced more successfully for total evaporation of bladder cancers with less anesthesia[6]. With the Thulium laser it became possible to perform an *en bloc* resection of superficial bladder cancer with a continuous wave laser beam instead of a pulsed laser beam of the Ho:YAG laser, which was seen as an advantage[31]. The Thulium laser technology offers an alternative for mono- and bi-polar electrosurgery for the treatment of superficial bladder cancer[29,31].
The Thulium laser was also used for the treatment of bladder outlet stricture in a small non-comparative study with satisfactory short-term results[32], and for resection of bladder neck obstruction without complications while two urethral strictures were observed in the electrosurgery group[33].

Kidney
Six clinical studies on open and laparoscopic partial nephrectomy for tumors were found in the search. In five studies the main objective was to evaluate the Thulium laser for the feasibility and effectiveness in partial nephrectomy surgery, and in one the Thulium laser was used for excision of the distal ureter and bladder cuff during nephroureterectomy[34–39]. Thulium laser partial nephrectomy appeared to be feasible and safe, with minimal blood loss for resection of the renal cortex exophytic renal tumors, for both open and laparoscopic surgery.

Urethra
The use of the Thulium laser for urethrotomy to treat strictures was first reported in 2009 by Feng et al. and Wang et al. and was found to be safe and effective[40,41].
The Thulium laser was also reported for the treatment of postoperative bladder neck contracture as an alternative for bladder neck incisions by cold knife incision (Sachse method), balloon dilatation, or transurethral resection[42].

In one study on 115 patients, the Thulium laser was compared with a Nd:YAG laser for the treatment of genital and urethral condylomata acuminata in males, concluding that the efficacy of the Thulium laser is comparable to the Nd:YAG laser but has a lower scarring rate in contrast to the Nd:YAG laser which has a deeper and less predictable laser-tissue effect[43].

Ureter
A case report described the ureteroscopic treatment of a benign polypoid lesion in the ureter, diminishing the risk of hemorrhage[44]. Another study compared treatment

for urethral fibroepithelial polyps between Ho:YAG laser and the Thulium laser. Both lasers were effective but the Thulium laser more effectively reduced the incidence of urethral strictures as a result of the urethral polyp resection with the Thulium laser[45].

The Thulium and Holmium lasers have also been compared for localized treatment of upper urinary tract urothelial tumors. Both lasers performed equally with regard to recurrence free survival, but the Thulium laser had a better fiber-tip stability and precision, and reduced bleeding and mucosal perforation reduction[46].

Penis

Musi et al. published the first study in which the Thulium laser was used for the treatment of 26 patients with penile cancer. Treatment was safe, easy and effective, comparable to CO_2 and Nd:YAG laser treatment and minimizing bleeding[47].

ENT: Ear Nose and Throat

Zeitels et al. used the Thulium laser for effective treatment of a wide range of endolaryngeal lesions such as papillomatosis, microinvasive carcinoma, benign supraglottic lesions, edema and granuloma under both local and general anesthesia[48,49]. Two small studies satisfactorily used Thulium laser in the treatment of laryngotracheal clefts in children[50,51].

Pothen et al. compared the Thulium laser (2013nm) with monopolar electrosurgery in patients with squamous cell carcinoma tumor in the oral cavity and concluded that thermal damage is comparable between both energy delivery devices[52].

Kamalski et al. described a nonrandomized comparison of the Thulium laser and CO_2 laser for primary stapedotomy for otosclerosis and concluded that the Thulium laser resulted in a higher chance of inner ear damage[53].

The effect of using the Thulium laser for transoral robotic surgery (TORS) was clinically evaluated in two studies with low patient numbers. Van Abel et al. claimed that TORS is feasible and safe and TORS resulted in fewer intra operative pharyngotomies and less post-operative pain[54]. Benazzo et al. concluded that TORS was feasible and showed promising results, due to the exceptional visualization and the tangential and angled incisions that can be made in contrast to the CO_2 laser[55].

Lungs

In the study of Scanagatta et al. in pulmonary resection surgery, the Thulium laser had the best result regarding the depth of thermal damage compared to electrosurgery and a 1318nm Nd:YAG laser[56]. In a follow up study, they did not recommend the use of the Thulium laser for anatomic pulmonary resections due to the occurrence of late pneumothorax even in the absence of postoperative air leaks[57]. Marulli et al. compared 40W continuous wave Thulium laser through a 550μm laser fiber on a stainless-steel hand piece in non-contact modus and mechanical stapling group. They concluded that Thulium laser pulmonary resection is feasible although the time-consuming nature of the procedure, high investment, and the need for a high-performance smoke evacuator and protection goggles were disadvantages[58].

Gesierich et al. described a study in which a Thulium fiber laser was used to resect endobronchial lesions. This study described a series of 132 patients and 135 resected lesions. 81 lesions were completely vaporized, 82 lesions were treated by deep tissue destruction followed by mechanical resection. Tumor bleeding was coagulated with effective hemostasis power settings between 5 and 20W were found to be safe. Also, in stent restenosis and the removal of stents after severe tissue granulation was treated safely[59].

Gastrointestinal

Four small studies described the use of the Thulium laser for endoscopic submucosal dissection (ESD) for gastric epithelial neoplasia and endoscopic myotomy. A important advantage was that only one instrument was needed for hemostasis and ablation of superficial mucosal lesions. The production of smoke was a problem during the procedures[60–63].

Gynaecology

A study of Davis et al. described a study in 12 female patients who underwent an endoscopic excision a polypropylene suture/mesh around the bladder neck. In some cases the polypropylene suture/mesh caused bladder perforation (2.5% to 11.7%) and mesh or suture erosion (0.6% to 5.4%). Eroded mesh/suture has to be removed and this initially had to be performed by an open cystotomy or with endoscopic electroresection/scissors. The Thulium laser was explored as an alternative for open cystectomy or transurethral electrosurgical resection for removal of eroded mesh material from the lower genitourinary tract after tension free vaginal tape suture/mesh treatment for stress urinary incontinence. The authors concluded that endoscopic

laser mesh excision might be an acceptable first line approach for the management of eroded biomaterials due to its high success rate and minimally invasive nature[64].
Henes et al. found the Thulium laser to be a good alternative for the CO_2 laser for the treatment of condylomas, cervical, vaginal and vulval neoplasias[65].

Breast

In one feasibility study the Thulium laser was used in ductoscopy for the treatment of intraductal breast neoplasia. Intervention in the milk ducts is challenging due to its small dimensions in the ducts and in the working channel of the ductoscope (0.45mm) The use of the Thulium laser was feasible and provides a new energy delivery device in ductoscopy[66]

Neurosurgery

The Thulium laser was explored as an instrument for endoscopic neurosurgery[6]. Both laboratory and clinical studies have been reported for neuroendoscopy. In a study including > 100 patients, the Thulium laser was appreciated as an effective and safe instrument because of low heat penetration in the aqueous medium or in irradiated tissue, for making a fenestration in the floor of the third ventricle for the treatment of hydrocephalus[8,68,69].
Also, one technical note described the endoscopic disconnection of hypothalamic hamartomas in people with drug-resistant epilepsy in 7 patients compared in a study with monopolar coagulation. The authors stated that the Thulium laser was able to obtain a finer cut compared to standard monopolar coagulation[70].

The other studies described mainly open cranial surgery for the treatment of meningiomas. Passacantilli et al. described the most extensive study with 20 cases and concluded that the Thulium laser was safe due to its narrow tissue penetration and particularly useful in resections of the falx and the tentorium[71,72].

Dermatology

The 1927nm Thulium fiber laser was used for exploring the effects of non-ablative techniques in skin rejuvenation and the treatment of melasma[73,74]. Boen et al. reported 60% to 90% improvement in male patients with solar damage to the scalp. Also, other dermatologic conditions were treated such as macular seborrheic keratosis on the neck, chest and extremities. The authors claimed that the non-ablative Thulium fiber laser technology could have a role in aesthetic skin rejuvenation as well as treatment and prevention of actinic keratosis.[75].

DISCUSSION

Electrosurgery versus Thulium laser

In this overview, we discuss the experience with the Thulium laser in clinical practice since its introduction in 2005. The Thulium laser has turned out to have specific benefits over electrosurgery. A disadvantage of electrosurgery is the lack of control over the path of the electric current. The electric current follows the path of lowest resistance causing unintended thermal damage in surrounding tissues or even major injuries (e.g. burns) to the patient[76–78]. For example, intra- and extracellular fluids like tissue water and blood have a lower electrical resistance than solid tissues[79]. The current will penetrate deeper into the (micro)vasculature which is beneficial for hemostasis but will take a longer time for tissue healing. With the use of the Thulium laser, heat is generated by absorption of light near the tip of the fiber only.

In addition, electrosurgery induces muscle contractions when applied directly to muscular tissue. This makes the Thulium laser an attractive alternative for precise bloodless muscle cutting like the tongue without contractions[52,80].

Clinical acceptance and clinical outcome

The Thulium laser is mostly used in the surgical specialties for soft tissue resections. In the urology field, the Thulium laser has been widely accepted in the treatment of BPH and has proven its efficacy[81].The number of scientific papers for other urological applications is increasing. Urologists have always been early adopters with laser technology and now urologists are expanding the working field of the Thulium laser. Except for the Thulium BPH application, most other papers concern case studies or feasibility studies with small numbers of patients, and conclude that larger randomized controlled multicenter trials need to be performed to gather proof of the efficacy and improvement of clinical outcome variables[82]. To further acceptance of the Thulium laser in clinical practice, randomized studies are needed comparing Thulium laser with golden standards such as electrosurgery.

Thulium laser compared to other lasers

Between available lasers, both the Thulium and CO_2 lasers have water as the primary energy absorber[48,65]. However, the Thulium laser has the major advantage that the energy is fiber delivered enabling endoscopic treatments. Furthermore Thulium (fiber) laser systems are compact and easier to handle compared to relative larger CO_2 lasers with vulnerable articulated arms as delivery system[65]. In general Thulium are less costly than CO_2 laser systems but still more expensive than electrosurgical units.

Potential applications for Thulium laser

Other areas where we expect the Thulium laser to gain wider application are endoscopic treatment of breast intraductal neoplasia. Thulium laser fiber technology enables to guide energy through very thin (370μm) laser fibers and thus a safe energy delivery device is available for intraductal intervention[66]. In future, it might be possible to ablate the complete ductal epithelium or ablation of precursor lesions as a primary form of primary prevention of breast cancer. Also, pancreatic intraductal neoplasia, esophageal mucosectomies, could be evaporated with the Thulium laser. Endoscopic equipment is becoming more sophisticated (chip on tip technology). Therefore, difficult to reach areas such as pancreatic- and bile ducts can be inspected more carefully and the need for refined energy delivery devices increases. The Thulium laser would fit in very well in the strongly endoscopic developing field of gastroenterology.

Endoscopically, it is theoretical possible to use the Thulium laser for all sorts of ablation purposes, in air, but also in an aqueous environment. Standard endoscope working channels often have sufficient space for commercially available laser fibers. Endobronchial lesions are very suitable for Thulium laser treatment. Also, bronchial strictures that can occur after lung transplantation can be treated.

In gynaecology, the Thulium laser could be used for the hysteroscopic resection of myomas. Hysteroscopic interventions are very common and Thulium laser fibers fit through the working channel very well. As the uterus is a muscle, Thulium laser resection avoids contraction, compared to electrosurgery. Other gynaecological hysteroscopic applications could be the treatment of polyps, adhesions, septum resections, isthmoceles. Endometriosis can be treated laparoscopically with the Thulium laser. For open laser surgery, condyloma (acuminata) are treated with the Thulium laser and forms a promising good alternative for the expensive and user-unfriendly CO_2 laser[83].
The question arises why the Thulium laser has not been generally accepted in other specialties than urology. First, BPH treatment with the Thulium laser as major advantages over electrosurgery, such as prevention of the TUR syndrome and reduction of blood loss and operating time[21–24]. For urology there was a clear need for improvement. Second, in other specialties, energy delivery devices as electrosurgery in both monopolar and bipolar modus dominate due to its proven effect and low costs. Why change a winning team? Early adopters in other specialties than urology are now discovering the benefits of the Thulium laser, especially in the treatment for intra oral tumors, in the ENT specialty.

Improvement of Thulium laser delivery and methods

Several technical developments are needed to further facilitate Thulium laser treatment. Thulium laser surgery in the "open" modus creates surgical smoke. For electrosurgery, sophisticated smoke evacuation devices exist, but these are lacking for "open" laser surgery. There is a need for a novel laser fiber handpiece for open laser surgery with integrated smoke evacuation. Also, the laser fiber laparoscopic applicators are scarce. Thulium laser laparoscopy and hysteroscopy would be more attractive if there was a broader range of fiber holder instruments available.

Limitation of the Thulium laser

Studies discussing the limitation regarding the coagulation/hemostasis using the Thulium laser in soft tissues when cutting through larger vessel diameters (mm) are minimal. Many studies describe successful feasibility studies, but no basic research has been performed for determining safety margins of blood vessel coagulation without clamping. Especially in organs with small capillary blood vessels and large diameter arteries like the kidney or liver tissue, one should always be careful not to cut through vessels thicker then approximately 1.5 to 2mm. However, no exact proof underlies this statement except for experience in daily practice. Of course, many parameters determine the degree of a successful coagulation such as diameter, blood pressure, type of vessel (vein or artery). Thulium laser users should be informed and instructed well before using the equipment clinically.

CONCLUSION

Most clinical experience with the Thulium laser treatments has been gained in urology and it has been well accepted for treating BPH. Other specialties have started clinical feasibility studies with promising results, however, controlled studies with larger number of patients are needed. The Thulium laser has the potential to become a successful surgical energy device as alternative for electrosurgery within multiple specialties especially for endoscopic applications as the fiber fits well through nearly every working channel. For open laser surgery, a combination with well-designed affordable hand piece with integrated smoke evacuation, would make the Thulium laser an attractive instrument.

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2

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3

THULIUM LASER-ASSISTED ENDOSCOPIC THIRD VENTRICULOSTOMY:

determining safe laser settings using in vitro model and two-year follow-up results in 106 patients

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ABSTRACT

Background and Objective

Endoscopic third ventriculostomy is used to treat hydrocephalus. Different laser wavelengths have been proposed for laser-assisted endoscopic third ventriculostomies over the last decades. The aim of this study was to evaluate Thulium laser endoscopic third ventriculostomy heat penetration in the surrounding environment of the floor of the third ventricle in an in vitro setting with visualisation of thermal distribution. Subsequently 106 Thulium laser endoscopic third ventriculostomy procedures were retrospectively analysed to demonstrate safety.

Methods

The in vitro visualisation was based on the color Schlieren method. The heat penetration was measured beneath a tissue phantom of the floor of the third ventricle with a fiber of 365μm in diameter at different energy settings; 1.0W (956J/cm^2), 2.0W(1912J/cm^2), 4.0W(3824J/cm^2), and 7.0W(6692J/cm^2), with a pulse duration of 1.0s. All experiments were repeated 5 times. In addition, 106 Thulium laser endoscopic third ventriculostomy procedures between 2005 and 2015 were retrospectively analysed for etiology, sex, complications and laser parameters.

Results

In the energy settings from 1.0 to 4.0W, heat penetration depth beneath the phantom of the third ventricle did not exceed 1.5mm. The heat penetration depth at 7W, exceeded 6mm. The clinical overall success rate was 80% at the 2-year follow-up study. Complications occurred in 5% of the procedures. In none of the 106 investigated clinical patients bleeding or damage to the basilar artery was encountered due to Thulium laser ablation.

Conclusions

The in vitro experiments show that under 4.0W the situation is considered safe, due to low penetration of heat, thus the chance of accidently damaging critical structures like the basilar artery is very small. The clinical results show that the Thulium laser did not cause any bleeding of the basilar artery, and is a safe technique for laser endoscopic third ventriculostomy.

Keywords: Endoscopic; fenestration; hydrocephalus; thermal damage;
third ventriculostomy; Thulium laser

INTRODUCTION

Over the last decades, endoscopic third ventriculostomy (ETV) is increasingly used for the treatment of hydrocephalus[1,2] Different techniques exist to fenestrate the floor of the third ventricle[3]. The most frequently used techniques are based on mechanical force by puncturing the floor of the third ventricle with a blunt or sharp instrument[3,4]. Subsequently the small opening is dilated with an inflatable balloon or endoscopic forceps[5,6]. Also electrosurgery is reported for puncturing a hole in the floor of the third ventricle[7].

Alternatively, laser techniques are used more commonly for ETV, but all fenestration techniques harbour the risk of damaging deeper structures[8–13]. The basilar artery is in close vicinity (within a few mm) of the floor of the third ventricle and damaging it is the most feared complication.

Different kinds of wavelengths have been proposed and used for laser-assisted endoscopic ventriculostomy (LA-ETV)[8,11,12,14]. Earlier studies show that an 810nm laser can be safely used in combination with a carbon layer on the tip of the laser fiber that absorbs all the laser light with pulse lengths of 1.0 s at 1-2.0W. The fiber tip reaches temperatures which ablate the tissue in direct contact[8,11,12]. This carbon layer coating prevents laser light from penetrating deeply into normal tissue. Without the carbon layer the 810nm laser light will penetrate approximately 8mm into unpigmented tissue[12]. If the carbon layer is slightly damaged there would be a higher risk of exposing laser energy to structures under the floor of the third ventricle. Also, the carbon coating has to be applied by the hospital since these fibers are not available on the market. So there is no controlled quality check on the degree of absorption[8,12].

In 2005 the 2.0μm Thulium laser system was introduced for soft tissue applications. Since then the 2.0μm laser is being used in fields like urology and ENT and appreciated for the superficial heat penetration[15,16,17,18]. The Thulium laser light can be transported through thin and flexible optical fibers (fiber optical core of 365 and 550μm), and is often used in e.g. endoscopic urological procedures for laser enucleation and vaporization of the prostate[19,20] Also, a few centers in the world use the Thulium laser for endoscopic neurosurgery, mostly for hydrocephalus, but also for septostomies and as a tool for coagulation of small capillary bleedings after taking biopsies[10,21]. The Thulium laser is also used for the resection of meningiomas in open cranial surgery[22]. For the treatment of hydrocephalus in our clinic, laser settings between 1.0 and 2.0W (set value on the laser apparatus) with a pulse duration of 1.0s are typically used. The laser fiber is in contact with floor of the third ventricle. There is no contraindication for performing a Thulium LA-ETV for a small distance between the basilar apex and the third ventricle floor. Sometimes when the floor of the third ventricle is thick or tough, longer pulse durations are used. Some authors claim that in an aqueous medium the laser effect is restricted to <2mm in front of the laser fiber tip[21].

The 2.0μm wavelength is predominantly absorbed in water (aqueous environment) and the transmission of the laser light and therefore heat in the cerebrospinal fluid (CSF) is low[10]. These two characteristics make this wavelength suitable for LA-ETV without damaging underlying structures, as compared to lasers that have less in water such as the KTP, Nd:YAG and the 810 nm diode laser[8].

Due to the strong local heating effect of the Thulium laser, tissue will already coagulate and ablate close to the fiber tip, temperature rise is very local and thus damage over lager areas is prevented[10]. The aim of this study is to visualize the mechanism of the coagulation/ablation effects of the Thulium laser with different laser settings. This will give insight, which laser parameters are preferred for Thulium LA-ETV on the floor of the third ventricle in relation to safety towards surrounding structures.

METHODS

In vitro model

To study the thermal effects of the Thulium laser a tissue model of the third ventricle was developed which could be placed in a Schlieren setup. In the Schlieren setup, thermal effects were visualized imaging the extent of temperature gradients in the tissue model, in a qualitative way (figure 1)[12,23]. By adding a metric scale to the setup, it is possible to determine the extent of the temperature gradient (heat penetration depth [mm]) underneath the in vitro tissue model of the floor of the third ventricle. This method enables the visualization of the dynamics of the temperature gradient during and after the laser pulse in a real-time video recording. The thermal gradient was expressed in color patterns (figure 4). In contrast to thermal cameras which can show only temperatures at a tissue surface, this method enabled visualization of thermal gradients inside an aqueous environment. A limitation of this method is the lack of showing absolute temperatures, however it perfectly shows the discrete region of a temperature gradient between room temperature and 100°C.

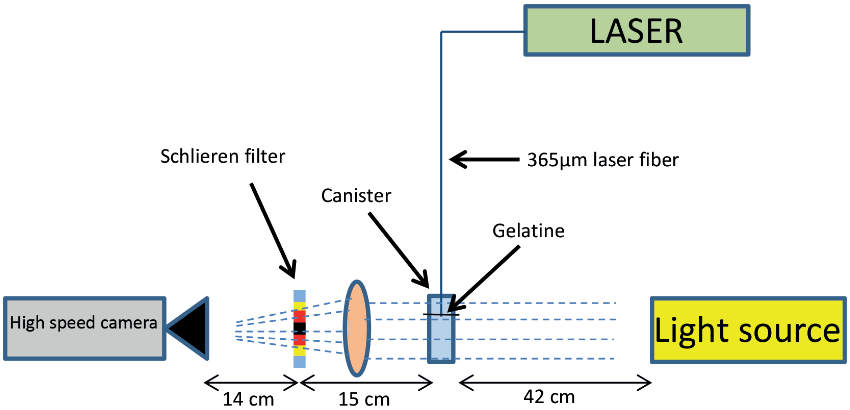

FIGURE 1. The color Schlieren setup with in vitro model (canister) of the floor of the third ventricle. The gelatin in the canister represents the floor of the third ventricle. The high-speed camera captures "thermal" images which show thermal differences qualitatively.

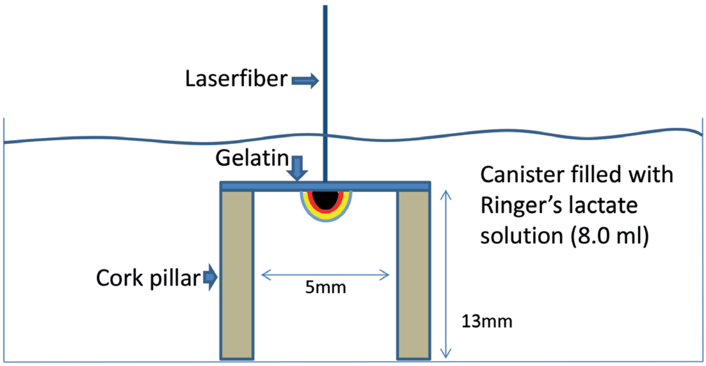

FIGURE 2. Schematic figure of the in vitro model. The gelatin layer functions as floor of the third ventricle. The gelatin is positioned on the cork pillars. For each different laser pulse a new piece of gelatin was used.

The measurement setup consisted of a canister filled with Ringer's lactate solution at room temperature (figure 2). This is the same infusion liquid that is used in a clinical setting during a LA-ETV. The volume of the Ringer's lactate solution was 8.0ml. The dimensions of the canister were 70mm x 6mm x 22mm. In the middle of the canister two cork pillars were positioned creating a small space representing the space around the floor of the third ventricle (figure 3). The width of the pillars was set on 5mm based on the average width of the third ventricle[24].

On top of the two pillars a sheet of gelatin was positioned as a tissue phantom of the floor of the third ventricle (figure 3). Gelatin was chosen as a tissue model because of the good reproducibility of the thickness and because of the protein presence. The thickness of gelatin was 0.44mm and represents the floor of the third ventricle of ETV patients, due to its denaturated form of collagen and high protein content[25,26].

For every laser pulse a new sheet of gelatin was used of 15mm x 5mm x 0.44mm. Prior to laser irradiation the gelatin sheet was immersed for 60s in the Ringer's lactate solution. This was done because gelatin absorbs fluid and eventually dissolves in water. The period of 60s was chosen to provide sufficient time to position a new sheet of gelatin in the setup for each individual laser pulse. Also, the period of 60s ensured a sufficient uptake of fluid in the gelatin, without being dissolved.

Laser system

A bare laser fiber (365µm Lisa Laser, Katlenburg-Lindau, Germany) was positioned in contact with the gelatin sheet. The laser fiber was connected to a laser with a

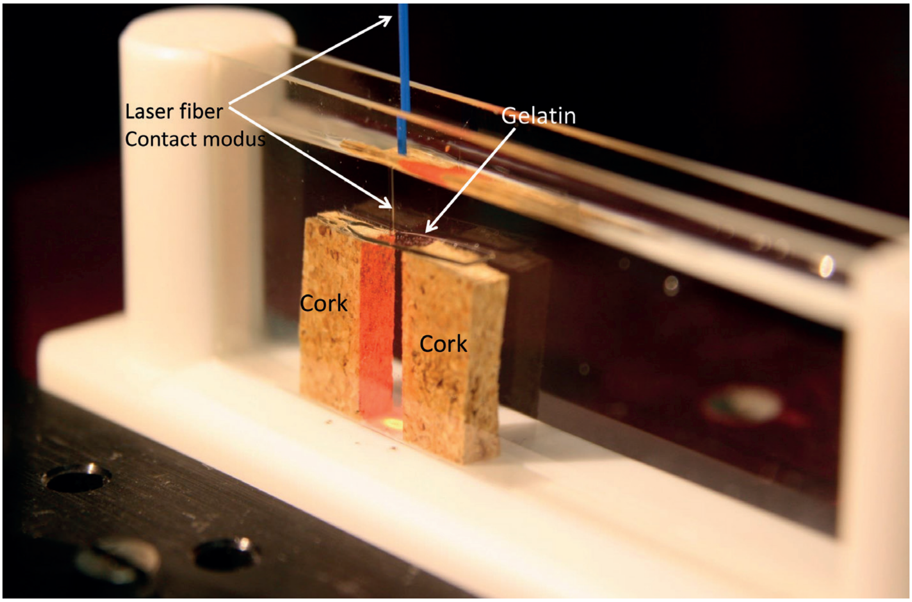

FIGURE 3. Setup of the gelatin sheet with laser fiber in contact with the gelatin sheet. The gelatin was positioned on the cork pillars, 60s prior to laser usage. In this way the water content of the gelatin was kept the same for all experiments.

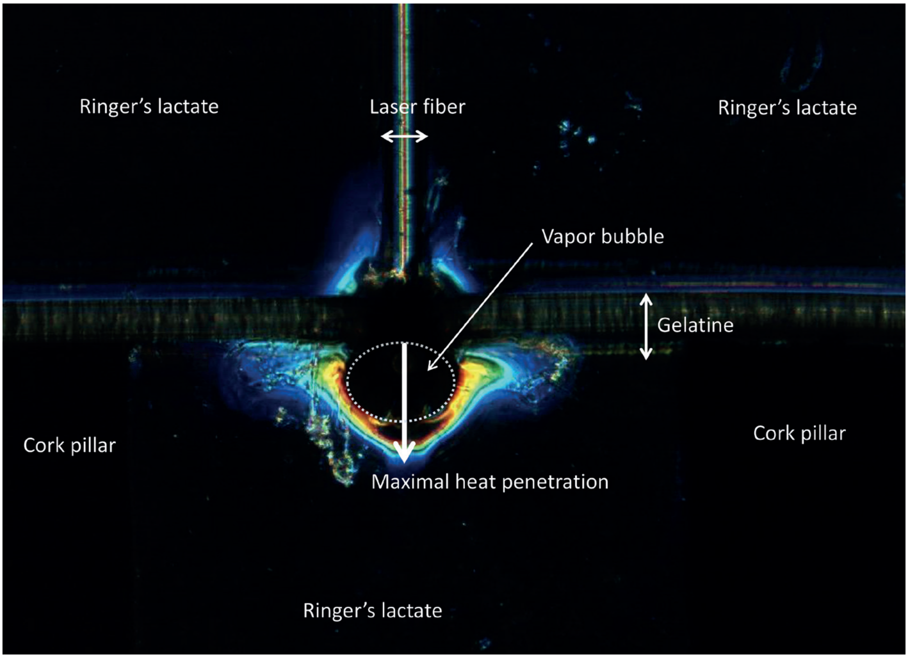

FIGURE 4. A typical video still of a color Schlieren image. The white arrow beneath the laser fiber and the gelatin indicates the maximal heat penetration beneath the gelatin. The black round structure in the dotted circle between the gelatin and the tip of the maximal penetration is a vapor bubble of 100°C. The maximal heat penetration was taken as parameter to express the heat penetration beneath the floor of the third ventricle.

wavelength of 2.0μm (Revolix Junior, Lisa Laser, Katlenburg-Lindau, Germany). The laser was set at four different power settings: 1W, 2W, 4W, and 7W. For reproducibility, the pulse duration was kept at 1.0s, and all experiments were repeated 5 times. In between each experiment the fiber was polished.

Camera setup

Video clips were captured with a high-speed camera (Mini UX50, Photron, Tokyo, Japan) at a frame rate of 1000 frames per second.

All video recordings were analyzed frame by frame and a snap shot was taken at the moment of steepest thermal gradient (figure 4). A reference video was made by adding a ruler with 0.5mm increments. Subsequently the mm scale was integrated in the snap shots with the steepest thermal gradient and the heat penetration was measured with ImageJ analysis software (ImageJ, National Institutes of Health, Bethesda, Maryland, USA).

Clinical data

To demonstrate the safety of the LA-ETV procedure a retrospective study was performed on the clinical outcome of 106 consecutive patients of all ages treated with Thulium LA-ETV between 2005 and 2015. Permission was obtained by the medical ethics committee of the University Medical Center Utrecht (WAG/mb/17/021369). All patient charts and operating reports were screened for (serious) adverse events like major bleeding per operatively. Also, the following characteristics were investigated: Power settings of the Thulium laser per operatively, the total amount of energy used during the LA-ETV, age at the time of the Thulium LA-ETV, sex, type of etiology of hydrocephalus and the two-year follow-up. Complications such as wound infection, meningitis, wound hematoma and wound dehiscence were documented. Also repeated LA-ETV and the percentage of patients that had to have a ventriculoperitoneal shunt (VP Shunt) were documented. A fenestration was marked as successful when an adequate communication was observed between the third ventricle and the prepontine cisterne. The 2-year follow-up was scored as successful if no VP shunt was needed in this period and no symptoms of hydrocephalus returned.

Statistical analysis

The data from the in vitro experiments were analyzed by calculating mean values and standard deviation. The power values of the clinical data were also analyzed by calculating mean values and standard deviation. The ETV outcome was marked as successful if the patient remained shunt independent over two years.

RESULTS

In vitro thermal visualization

The results from 1.0W (956J/cm^2), 2.0W(1912J/cm^2), 4.0W(3824J/cm^2), and 7.0W(6692J/cm^2) are summarized in figure 5. For every experiment, a single 1.0s shot was used. The laser fiber was positioned in contact with the gelatin. At all settings fenestration of the gelatin sheet was achieved, which was confirmed visually. For 1.0W the heat penetration depth is 0.44±0.03mm, for 2.0W 1.10±0.09mm, for 4.0W 1.43±0.12mm and for 7.0W 6.57±1.61mm underneath the tissue model.

As expected, the heat penetration depth increases with increasing power. At 7.0W the standard deviation increases considerably due to explosive vapor formation. In the pulses from 1.0W the heat penetration does not exceed 1.0mm, meaning that there is no rise in temperature below 1.0mm from the gelatin. From 2.0W to 4.0W a spherical

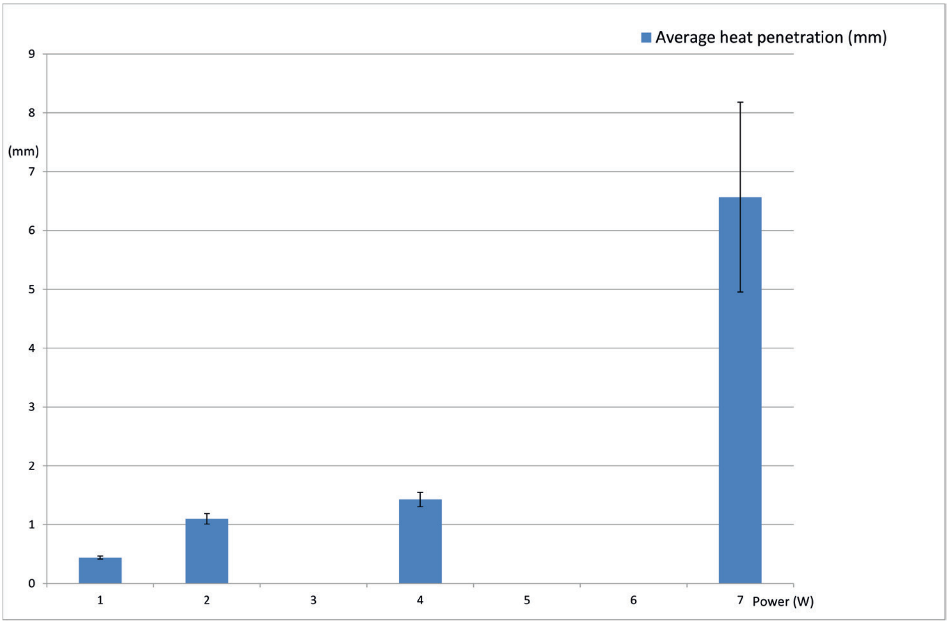

FIGURE 5. Shows the distance of the heat penetration with the different Thulium laser energy settings in the *in vitro* model in (mm) with the standard deviation. Each power setting was repeated five times.

vapor bubble is formed, but from 7.0W the bubble 'explodes' and subsequently a 'jet' of heated fluid is created through and underneath the gelatin (Figure 6). The jet formation causes an irregular fluid flow; hence the increased standard deviation. The tip of the jet was measured as parameter for the heat penetration underneath the gelatin.

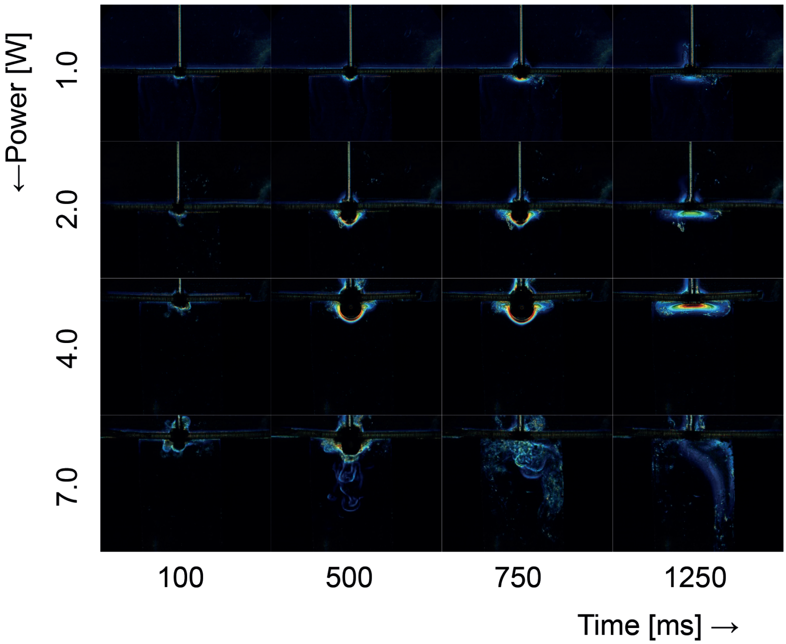

FIGURE 6. Thermal effects are shown for intervals at t=100ms, t=500ms, t=750ms and t=1250ms. At 1W there is very little heat penetration. At 2.0W and 4.0W a clear round shape vapor bubble arises due to heating of the Ringer's lactate. At 7.0W, a more turbulent irregular pattern was seen. Note that at 7.0W t=500ms a blue 'plume' appeares. This event is caused by laser irradiation through the vapor bubble with consecutive absorption in de Ringer's lactate. The total laser pulse was 1000ms. For the turbulent effects at 7.0W the complete light blue "plume" was measured as heat penetration parameter. From the 4.0W power setting and below no such turbulent effects are seen as with the 7.0W power setting. The video stills at 1250ms showed the cooling period after laser usage.

Clinical data

The characteristics of the included patients who were treated with the Thulium laser are presented in Table 1. 106 consecutive patients between 31 days and 78 years old underwent a Thulium LA-ETV between 2005 and 2015. None of these patients had any injury to the basilar artery, or other severe bleeding complications.

All of these patients had a successful fenestration, observed per operatively without complications during surgery. The average laser power used, was 1.7±1.0W with an average total energy of 145±129J and pulse length of 1.0s. The two-year follow-up is presented in Table 2. After two years 90 patients remained in the study, 16 patients died from progression of malignant disease.

1 patient had a repeated Thulium LA-ETV within 4 months after the primary procedure. There was no need for drains for this patient within the follow-up period of two years. From the 90 patients remaining in the study, 19% received a VP Shunt. The complication rate was 5% post operatively (Table 3.).

TABLE 1. Characteristics of 106 patients treated with Thulium laser ETV

Age	
Mean (standard deviation)	37 years (25)
Range	31 days-78 years
Sex	
Male	61 (58%)
Etiology	
Tumor	41 (43%)
Aqueductal stenosis	39 (38%)
Hemorrhage	4 (3%)
Cyst	8 (8%)
Normal pressure hydrocephalus	4 (4%)
Other	8 (8%)
Laser parameters	
Power setting: Mean (standard deviation) Power range:	1.7W, (1662J/cm^2) 1.0W,(956 J/cm^2) 1.0W (956J/cm^2)-3.5W (334J/cm^2)
Total energy used : Mean (standard deviation)	149J (129J)

TABLE 2. Success percentage 2-Year follow-up according to etiology.
Patients remaining in study: 90

	Number	%
Overall success percentage	**72**	**80**
Tumor	27	81
Aqueductal stenosis	39	77
Hemorrhage	4	75
Cyst	7	86
Normal pressure hydrocephalus	4	75
Other	8	100

TABLE 3. Complications reported for 106 patients after 106 Thulium LA-ETV procedures

Parameter	Number	%
Wound infection	0	0
Meningitis	3	3
Cerebrospinal fluid leakage	1	1
Wound hematoma	1	1
Wound dehiscence	0	0

DISCUSSION

In this study, the heat penetration of the Thulium laser was studied using a special optical setup mimicking the environment of the floor of the third ventricle. With all tested laser parameters, a fenestration was achieved in the tissue model. This visualisation showed that the heat penetration beneath the phantom representing the floor of the third ventricle is very small for the power settings of 1.0W and 2.0W (for 1.0W 0.44±0.03mm, for 2.0W 1.10±0.09mm). At higher power settings (4.0 and 7.0W), the heat penetration increased. At 7.0W the heat penetration exceeded 6.0 mm.

3

The Thulium laser has a reproducible effect in water at laser settings below 4.0W in the optical setup, i.e. the heat effect of the Thulium laser is limited to 1.43±0.12mm. The laser light is predominantly absorbed in an aqueous environment. As the ETV environment is mainly water, a laser with water as absorber is the most logical choice. In settings below 4.0W the Thulium laser irradiation stays close to the fiber tip, preventing damage to the surrounding tissue.

The experiments showed that it is important to limit the power below 4.0W. At 7.0W, explosive water vapor bubbles are formed inducing turbulence, hot water jets and thus increasing the in improbability of accidently heating critical surrounding structures (figure 6).

As can be expected the heat penetration beneath the tissue model becomes larger as power settings of the Thulium laser increase. The increasing uncertainty of the heat penetration at 7.0W can be explained by the more turbulent effects that arise from the 7.0W power setting (Figure 6). The turbulent events at 7.0W are completely different than the reproducible effect in laser settings up to 4.0W. The fluid turbulence at 7.0W results in a downward jet stream. Ebner et.al. claim that the heat penetration of the 2.0 µm wavelength does not exceed 2mm in water[21]. But these data are based on research performed with a pulsed laser (Ho:YAG) with single pulses between 50 and 800mJ at a pulse width of 600µs which is beneath the threshold for vapor formation[27]. This comparison cannot be made and it is visible with the in vitro setup that an increase in power of the Thulium laser causes heating of the deeper layers of the surrounding water due to dynamic bubble and jet stream formation. This is not limited to 2mm in water as Ebner et.al. claim.

In translating the results of the lab experiments to the clinical situation, there are aspects that are different compared to the clinical situation. One of the major differences is that the gelatin mimics the bottom of the third ventricle due to its protein content, but lacks fibrin which provides mechanical strength and resistance for penetration. Other tissue models have been tried like chicken-skin and real cadaver material, but all materials had the disadvantage of not being reproducible and therefore strongly influencing the outcome of the results. The flushing of the Ringer's lactate solution was not included as a parameter in the in vitro setup. In a clinical situation, the endoscopic environment is flushed with Ringer's lactate solution. However, there is no standard rate of flow and it differs between surgeons and situations. This flushing through the working channel of the endoscope functions as a heat sink. Theoretically, the clinical situation might even serve as a more optimal environment for Thulium laser usage.

The in vitro model has limitations as mentioned above, but it shows the effect of the Thulium laser in small spaces accurately. Gelatin has several advantages as a tissue phantom. Gelatin contains a very high protein content[26]. A disadvantage is the water uptake by the gelatin which may be variable over time. Therefore, a standardised time frame for soaking the gelatin was used to minimize this effect. The dry gelatine slices were soaked for 60 seconds to give the gelatin enough time to absorb an ample amount of water without dissolving.

The neurosurgical clinic in the University Medical Center Utrecht has accepted the Thulium laser as a useful instrument for LA-ETV. After a long and positive experience with the 'black tip' diode laser[8], the surgeons instantly appreciated the controlled ablation effect of the 2.0μm laser with the safety of the 'water shielding'. All ETVs are performed with the Thulium laser after 2005 without complications such as bleeding due to a puncture or rupture of the basilar artery. Compared to other studies, the results of the clinical parameters are similar[8,9].

Studies in which mechanical techniques have been evaluated in ETV, show low complication rate but these complications have not been described with Thulium LA-ETV[4,6,28]. The flexible laser fiber and good reproducibility of the thermal effect make the Thulium laser an attractive instrument for LA-ETV. The good reproducibility ensures a well-defined thermal damage. A hypothetical advantage of laser in general, compared to balloon dilatation could be that by evaporating parts of the floor of the third ventricle a more patent fenestration could be made due to cell destruction. With a balloon dilatation, the tissue is pushed aside, instead of vaporized. In order to investigate the difference between LA-ETV and balloon dilatation clinical studies could be performed in which these two techniques are compared and investigated.

The Thulium laser used is in the same price range a high-end electrosurgery unit. The cost of the disposable laser fiber is around 300USD however, a reusable version (25 times) is available which needs to be refurbished (cleaving of the tip, and resterilizing) between procedures.

CONCLUSIONS

The Thulium laser assisted ETV can be considered safe and reproducible due to a shallow heat penetration as proven by in vitro thermal imaging when the power settings are below 4.0W. The aqueous environment forms a natural shielding for deeper structures. However, at 7.0W thermal effects become unreproducible due to the formation of explosive water bubbles and hot water jets and thus should be prevented to protect critical structures like the basilar artery. In a consecutive series of 106 patients it was demonstrated that fenestration can easily be achieved within the 1.0-3.5W range. Thulium LA-ETV proved to be safe without complications and an 80% overall success after two-year follow-up.

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EX VIVO FEASIBILITY STUDY OF ENDOSCOPIC INTRADUCTAL LASER ABLATION OF THE BREAST

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ABSTRACT

Objective
To determine the feasibility and safety of breast endoscopic thulium laser ablation for treatment of intraductal neoplasia.

Study design
Ductoscopy is a minimally invasive endoscopic approach of the milk ducts of the breast via the nipple. Besides diagnosis in women with pathologic nipple discharge (PND), it allows non-invasive removal of intraductal lesions with a stalk like papillomas. Removal, however, is often incomplete and flat lesions cannot be targeted. We therefore developed laser ductoscopy.

Methods
Dosimetry of laser ductoscopy was assessed in thirteen mastectomy specimens, applying power settings of 1-5W with 100-1000ms pulsed exposure to a 375-μm outer diameter thulium fiber laser. Subsequently histology was obtained from the breast tissue that was treated with the Thulium laser.

Results
Endoscopic view was maintained during ductoscopic laser ablation at 1-3 W. Increasing power to 4-5 W caused impaired vision due to shrinkage of the main duct around the ductoscope tip. Histology revealed localized ablation of the duct wall.

Conclusions
We show for the first time that laser ductoscopy is technically feasible. The Thulium laser enables a superficial intraductal ablation and is a useful tool for intraductal interventions. An *in vivo* prospective study is needed to further demonstrate its potential.

INTRODUCTION

Pathologic nipple discharge (PND) is defined as spontaneous, single duct nipple discharge and is responsible for approximately 5% of surgical referrals to the breast clinic[1]. As PND might be associated with breast cancer, numerous women with PND undergo exploratory surgery to rule out malignancy and to treat symptoms. Breast cancer, however, is found in a minority (3-7%) of the referred women with PND and no other signs of malignancy at physical or additional examination[2–6], while benign intraductal papillomas are found in 53-84%[6–11].

Ductoscopy is a minimally invasive endoscopic approach with a fiberoptic endoscope. It enables direct access to the ductal system via the natural orifices of the nipple[12–14]. It has been proven to be a useful tool in the evaluation of patients with PND[6,11,15]. Moreover, intervention ductoscopy has shown to allow transductal minimally invasive removal of intraductal papillomas[6]. Therefore, interventional ductoscopy has the potential to replace surgery in patients with PND but no signs of malignancy during diagnostic workup. In our clinic ductoscopy procedures are performed on a weekly base and other hospitals are becoming more interested in setting up ductoscopy.

Current endoscopic interventional methods, however, are suboptimal. The 'basket'-intervention device[6,16–18] is not feasible for all lesion types nor for complete lesion removal since the lesion is torn of at the level of the stalk[6]. Other intraductal biopsy devices are not commercially available[19,20]. In our recent cohort study basket extraction was feasible in only a selected group in 41% of 82 patients with polypoid lesions[6]. Symptom resolution has been limited to 70% of the 27 patients in whom a lesion could be removed[6]. Flat intraductal cancer precursor lesions cannot be targeted.

In the current study we investigated *ex-vivo* the feasibility of transductal laser ablation through the ductoscope in thirteen mastectomy specimens (Figure 1).

The Thulium laser has a 2013nm wavelength and is predominantly absorbed in water with a shallow heat penetration in tissue.[21] This shallow heat penetration gives a good controlled localized effect[21]. The laser beam is transmitted through fibers in various diameters making it suitable for endoscopic procedures. It is used mostly in minimally invasive (transluminal) treatment of benign prostate hyperplasia. Earlier studies have shown that Thulium laser ablation is a safe instrument for tissue ablation[22,23]. The superficial heat production results in a localized tissue ablation zone, minimizing the risk of thermal damage in underlying tissue[24].

The primary aim of our study was to determine the feasibility of the Thulium laser in an *ex vivo* ductoscopic set up.

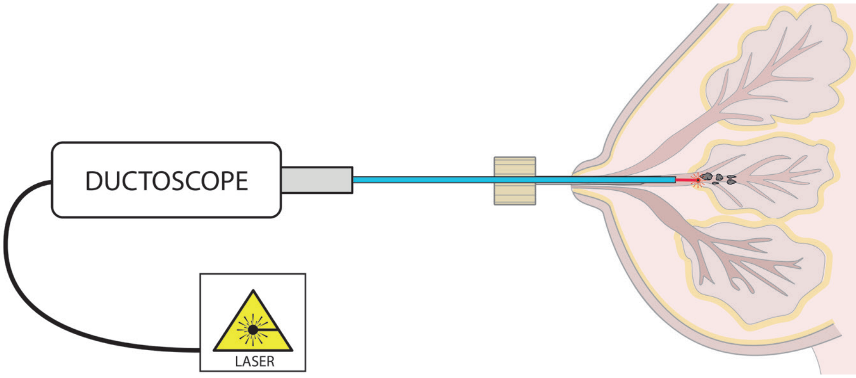

FIGURE 1. Schematic overview of an introduced ductoscope via the natural orifices of the nipple. A laser fiber is inserted in the working channel.

METHODS

To determine the optimal power settings for acquiring an adequate lesion diameter, an *ex vivo* study was performed.

Thirteen mastectomy specimens could be collected from patients with a diagnosis of breast carcinoma or high-risk of breast cancer who underwent a prophylactic or therapeutic mastectomy between May 2013 and November 2014 were recruited for the study. Mastectomy specimens from patients with previous surgery or radiotherapy of the breast were excluded since this might impair cannulation. This *ex vivo* study was approved by the Internal Review Board of the University Medical Center Utrecht. Since the study did not interfere with conventional diagnosis, the need for informed consent was waived.

All mastectomy specimens were examined freshly within 1 hour after surgical resection. The specimen was placed and stitch fixated onto a dome-shaped pad to spread the milk ducts for easier passage of the ductoscope. Salivary duct probes (Karl Storz, Tuttlingen, Germany) size 0000 to 1 and an obturator (Polydiagnost GmbH, Pfaffenhofen, Germany) were used for dilatation of the duct orifices in the nipple. The introduction port (SoLex-Nipple-Expander®, Polydiagnost) or a custom-made introduction port compatible with the Storz endoscope was placed into the duct orifice through which the ductoscope was introduced.

For the *ex vivo* procedure a 0.55mm optic (LaDuScope T-flex, Polydiagnost) inserted in a 1.15 mm outer diameter Polyshaft (PD-DS-1015, Polydiagnost), or a Storz miniature endoscope (Erlangen, Karl Storz) with incorporated fiberoptic light transmission and outer diameter of 1.1mm was used. Both devices are semi-flexible and have an combined irrigation channel for saline-infusion and a working channel (diameter 0.45 mm) via which the fiber was introduced.
Ductoscopic exploration was performed while avoiding the breast quadrant containing malignancy in order to prevent interference with patient diagnostics. At depths of approximately 4cm from the nipple orifice with clear view and normal appearing ducts, a bare-tipped single use low OH silica fiber (Tobrix, Waalre, The Netherlands) with a core diameter of 200μm and an outer diameter of 375μm (Figure 2) was introduced through the working channel. Laser energy was delivered using 2013nm thulium laser generator (Revolix Junior; LISA Laser Products, Katlenburg, Germany) at stepwise increased power settings of 1 to 5W with single pulses of 100-1000ms. The aiming beam was used at 85% for precise focusing at the duct wall.

In order to facilitate precise histological correlation in the last three specimens a marking wire (n = 2) (PD-AC-0061, Polydiagnost) or colour marker (n = 1) (sterile Black Eye Endoscopic marker™, The Standard, Korea) was placed under direct vision, through the working channel of the ductoscope at the level of the ablation. Ductoscopic images were recorded. All *ex vivo* ductoscopy procedures were performed by the same physician (LW).

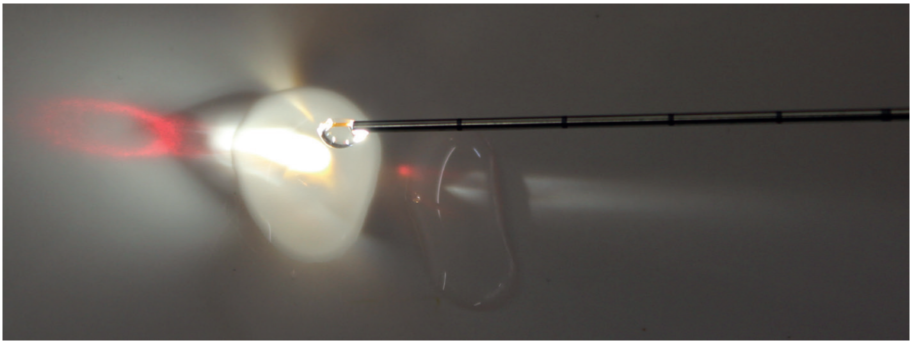

FIGURE 2. Tip of the laser fiber presented through a ductoscope (Karl Storz) with a red aiming beam. Stripe marks on the ductoscope represent 1 cm. The tip of the laser fiber can only be moved back and forth through the axis of the working channel. Aiming of the laser needs to be performed by manoeuvring the ductoscope.

After the *ex vivo* ductoscopy procedure the specimens were submitted fresh to pathology, where the margins of the specimen were inked. In specimens with intraductal dye-marking different colours were used in order to prevent interference with the intraductal dye-mark. The specimen was sliced in 5mm slices, searched for the marked area and macroscopic ablation lesions. At the level of the laser ablation where a marking wire or colour marker had been placed, the specimen was totally embedded at a transversal plane to acquire a trans sectional view of the duct. All tissue was formalin fixed and used for routine histopathological evaluation using conventional haematoxylin eosin (HE) staining. At the level of the tumour the specimen was embedded according to standard procedure.
The size of the ablation zone was evaluated. The histological effects of laser ductoscopy were assessed by a dedicated breast pathologist (PvD).

RESULTS

Ex vivo feasibility and optimization of the power settings

A total of thirteen mastectomy specimens from ten patients were studied. Cannulation of at least one duct could be achieved in nine specimens (82%) in eight patients. Due to technical problems laser ablation could not be performed in two specimens. Laser ablation was executed in the remaining seven specimens, using single pulses of 100-1000ms at 1, 2, 3, 4 and 5W. The laser fiber was smoothly introduced, leaving enough space for saline irrigation in the working channel. In five specimens multiple ablations were performed at different locations in a single duct system. In two specimens where more than one duct orifice was cannulated, ablations were performed in multiple ducts. Endoscopic view was maintained during laser ablation with 1-3W. At 3W shrinkage of a small ductal branch could be achieved (Figure 3). Increasing power to 4-5W caused impaired vision due to shrinkage of the main duct around the ductoscope tip.

Histology ex vivo study

Showing a coloured segment of the ductal system or an intraductal wire, the marking wire and colour marker both aided in macroscopic localisation of the treated duct, and the colour marker was also identifiable microscopically (Figure 4).

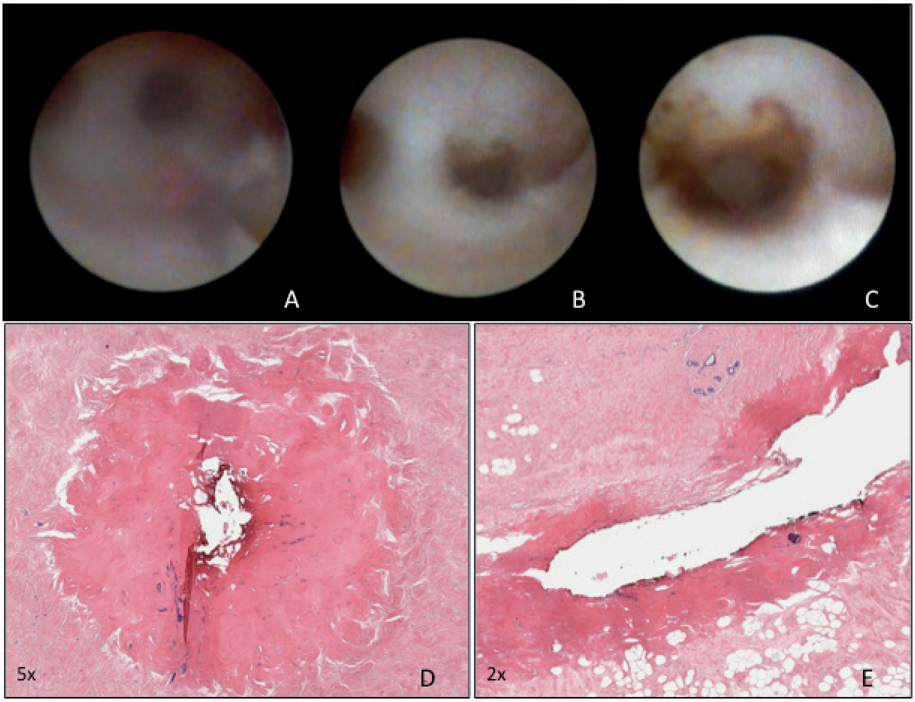

FIGURE 3. Ex vivo transductal laser ablation and subsequent histological assessment. Trifurcation of ducts with the tip of the laser fiber approaching from bottom right, aiming for middle duct (a). Laser ablation at 3W resulting in shrinkage of the middle ductal branch with endoscopic ablation effect (b). Close-up of the ablated middle duct (c). Histologic axial section (HE, 5x) of the duct showing completely destroyed ductal epithelium and deeply eosinophylic surrounding stroma as sign of ablated breast tissue with a central increase in intensity (d). Histologic transversal section (HE, 2x) of an ablated duct (e).

Macroscopically no ablation effects could be identified. Microscopically, in six (85.7%) of seven laser-treated mastectomy specimens one or more areas with ablation effects were localized. In one patient the location of ablation could not be found, although during ductoscopy the ablation effect was clearly visible.

Median thermal damage depth was 1.0mm, ranging from 1.0 to 2.0mm. An example of the pattern and depth of thermal damage after a resection with thulium laser is shown in Figure 2. Based on the properties of endoscopic-control and low penetration depth, transductal thulium laser ablation was deemed safe for *in vivo* use at settings of 1-5W.

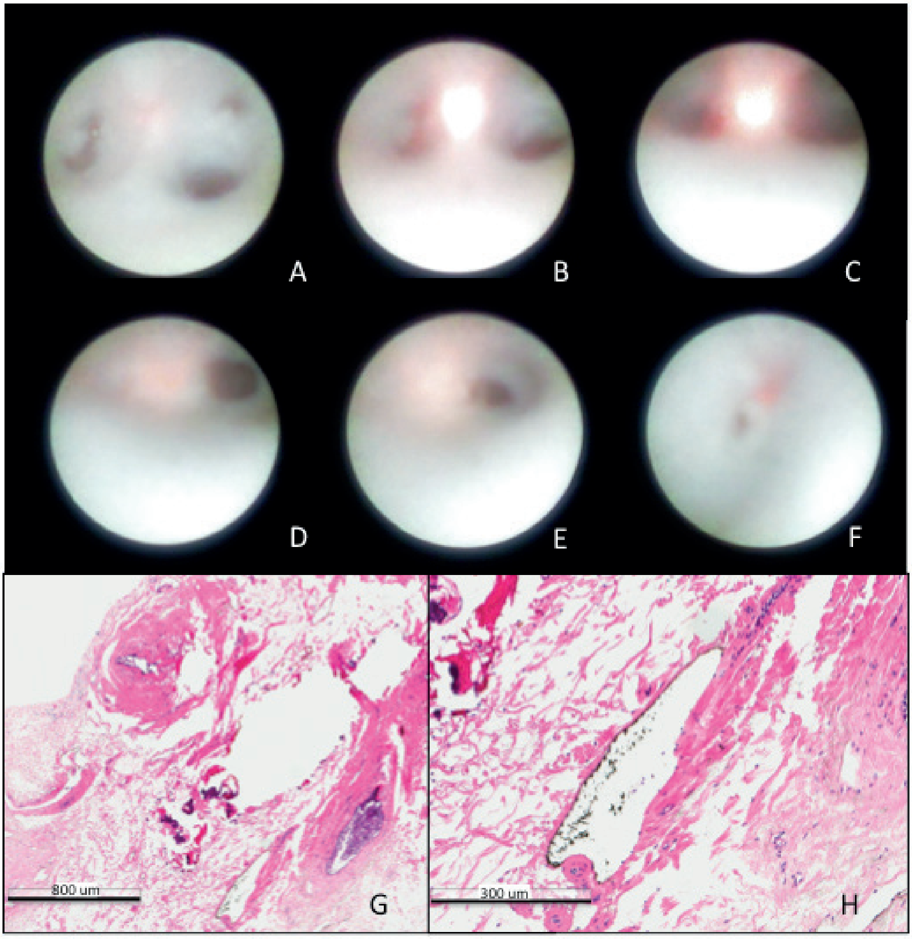

FIGURE 4. Ex vivo transductal laser ablation resulting in shrinkage of a ductal branch, followed by intraductal dye-marking and subsequent histological assessment. After removal of the fiberoptic, marking dye was inserted through the polyshaft. Duct trifurcation (a). Laser fiber tip appearing from above (b). Laser ablation at 3W (c). Ductal branch disappearing after ablation (d). Ongoing ablation (e). Shrinkage of the second ductal branch (f). Histology (HE) overview with ablated zone (g). Histology (HE) of ablated duct with intraductal black marking locating the ablated duct (h).

DISCUSSION

The aim of this study was to assess the feasibility of ductoscopic laser treatment for intraductal papillomas causing PND. The *ex vivo* study showed that ductoscopy with transductal Thulium laser ablation is feasible.

Previous studies have touched upon the therapeutic consequences of diagnostic tissue collecting via ductoscopy but also showed its limitations. The used biopsy devices are not yet commercially available[19,20]. Lesion extraction with the "basket device" can inherently not always achieve complete removal and is restricted to a selected group of polypoid lesions. Although the procedure has been suggested previously[25,26], data on laser ductoscopy were not reported before.

The main advantage of ductoscopy for localization and treatment of intraductal neoplasms are reduction of the need for surgery for a benign cause, conservation of breast tissue and nipple function, better cosmesis and fewer complications (approximately 5% wound complications for microdochectomy and major duct excision[27], 15% for microdochectomy in our hands, unpublished results[6]).

Before this novel minimally invasive treatment strategy can be implemented in a routine clinical manner, it is important that the benign nature of the intraductal lesion causing the symptoms can be reliably assessed. There are contradictory views about the correlation between intraductal visual observations and histological diagnosis. While some studies reported a significant correlation[28,29], others found no specific data except for gross morphological abnormalities such as papillomas[9,11,30–32]. Although the sensitivity of ductoscopy in PND with non-suspicious imaging is reported to be as high as 88-99%, specificity remains questionable at 20-85%[7–9,11,29,33]. The basket device is useful for tissue diagnosis in polypoid lesions, with successful (partial or complete) removal in 63-79% of attempts[6,31]. For superficial epithelial lesions or small or obstructing polypoid lesions basket extraction is not feasible[6,16–18]. For ductoscopic diagnosis and assessment of suitability for laser ablation therefore a commercially available device to facilitate adequate intraductal biopsy and subsequent diagnosis is eagerly awaited. Diagnostic accuracy may also be improved with advanced imaging techniques such as optical coherence tomography (OCT)[34-36] or autofluorescence[37-39] or by complementing ductoscopy with assessment of cytology or promoter methylation of ductoscopy-directed ductal (brush) lavage fluid[40–43].

As sensitivity of directed breast imaging improves, the amount of patients with PND and negative imaging should decrease, as should the likelihood of malignancy within this population. Among modern series of patients presenting with PND with negative physical examination and both negative mammography and diagnostic ultrasound, the incidence of malignancy on duct excision was 2-4%, leading the authors to advise a conservative approach[5,44]. Moreover, due to lesions in the periphery of the breast being missed, conventional surgery in the form of major duct excision or microdochectomy is not the perfect diagnostic standard[27,45]. To treat benign symptoms of PND ductoscopic diagnosis and intervention with basket extraction and/or subsequent laser ablation provides a potential promising minimally invasive approach. Also for symptomatic selective treatment of affected ducts laser ductoscopy may be of use; the use of higher power levels caused shrinkage and thereby complete occlusion of the main duct. A potential future application may be the complete ablation of the ductal epithelium or ablation of precursor lesions as a form of primary prevention of breast cancer.

The diameter of the ductoscope is in our experience not a limitation for inspecting beyond the central duct. In our experience most side branches can be inspected as the diameter of the branches do not decrease rapidly when proceeding deeper into the breast.

CONCLUSIONS

This *ex vivo* study has shown for the first time that laser ductoscopy is technically feasible and can serve as an important adjuvant tool for minimally invasive treatment of intraductal papillomas in patients with PND without imaging abnormalities. A large-scale prospective study is needed to demonstrate the potential of this novel approach including analysis of cost-effectiveness. Since endoscopic diagnosis of intraductal lesions is not always possible, optimization of ductoscopic diagnostic instruments is warranted.

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1470NM DIODE LASER IN STAPEDOTOMY; MECHANICAL, THERMAL, AND ACOUSTIC EFFECTS

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ABSTRACT

Background and Objectives

Multiple laser systems have been investigated for their use in stapes surgery in patients with otosclerosis. The diode 1470nm laser used in this study is an attractive laser system because it is easily transported and relatively inexpensive in use. This wavelength has relative high absorption in water. This study aimed to investigate the mechanical, thermal, and acoustic effects of the diode 1470nm laser on a stapes in an inner ear model.

Materials and Methods

Experiments were performed in an inner ear model including fresh frozen human stapes. High-speed imaging with frame rates up to 2000 frames per second (f/s) was used to visualize the effects in the vestibule during fenestration of the footplate. A special high-speed color Schlieren technique was used to study thermal effects. The sound produced by perforation was recorded by a hydrophone. Single pulse settings of the diode 1470nm laser were 100ms, 3W.

Results

Diode 1470nm laser fenestration showed mechanical effects with small vapor bubbles and pressure waves pushed into the vestibule. Thermal imaging visualized an increase temperature underneath the stapes footplate. Acoustic effects were limited, but larger sounds levels were reached when vaporization bubbles arise and explode in the vestibule.

Conclusion

The diode 1470nm laser highly absorbs in perilymph and is capable of forming a clear fenestration in the stapes. An overlapping laser pulse will increase the risk of vapor bubbles, pressure waves and heating the vestibule. As long as we do not know the possible damage of these effects to the inner ear function, it seems advisable to use the laser with less potential harm.

Keywords

Otosclerosis; inner ear; diode laser; hearing loss.

INTRODUCTION

Stapedotomy is a frequently performed specialized procedure to improve hearing by reducing the air bone gap found in patients with otosclerosis[1,2]. As part of this procedure a fenestration is made in the footplate. This is probably the most critical step and not without risks for inner ear damage. This is traditionally done with a burr systems like the Skeeter drill or micro pick instruments. The first non-contact laser in stapedotomy was described in 1980[3]. Up to now, multiple laser systems and various surgical techniques have been proposed. Laser systems are also being used with potential advantages such as reduced mechanical trauma. Not all lasers are the same and different wavelengths and settings will have its influence on water absorption coefficients and heat and sound characteristics. However, with these different laser systems and their own characteristics potential adverse effects should also be recognized.

The variety in medical laser systems and their specific wavelengths have different laser-tissue interaction and therefore unique effects. For example, Argon (488nm), diode laser (980nm), and KTP laser (potassium titanyl phosphate, 532nm) with low water absorption coefficients have been used in pigmented tissues, or haemoglobin-rich tissues[4]. When using these lasers to perform fenestration of the stapes footplate ultimately some of the laser light will pass through the osseous layers of the footplate and escape into the space below. The "residual energy" of this type of laser will barely be absorbed in watery liquids such as the perilymph after fenestration the footplate in stapedotomy. Theoretically, the KTP laser could generate heat in rich pigmented areas of the neuro-epithelium of the vestibule due to light transmission through the perilymph. However, the KTP laser and the 980nm diode laser parameters which are typically used in for stapedotomy are unlikely to damage inner ear structures directly [5,6]. These lasers appear to be safe in a clinical setting.

A variety of laser systems in the infrared spectrum have water as primary energy absorber. The Thulium laser (2010nm), Er:YAG (erbium-doped yttrium aluminum garnet, 2940nm) and CO_2 laser (carbon dioxide, 10600nm) are well absorbed in water. Excess energy is highly absorbed by perilymph and will not reach the neuro-epithelium in stapedotomy[7,8]. The absorption of energy in water causes heat and bubble formation. The explosion and the implosion of these vapor bubbles creates pressure waves in the vestibule[9].

Diode lasers are electrically pumped semiconductors and are able to produce coherent radiation. These diode lasers are available in different kinds wavelengths. They are fiber delivered, small, and relatively inexpensive. The first report of a diode laser (808 nm and 812nm) in otorhinolaryngology originates from 2000[10]. The most common diode lasers have been used in medical practice provide wavelengths between 800 to 1064nm. Recently, a new diode laser device emitting a wavelength of 1470nm has been successfully applied in minimally invasive treatment of incompetent saphenous veins, hyperplastic inferior nasal turbinates, tonsillotomy, benign prostatic hyperplasia treatment, lipolysis in arm contouring, and anal fistula-tract closure[11-16]. So far, there has been no information about the application of the 1470nm diode laser for stapedotomy. This laser might have similar results compared to the Thulium laser (2000nm). The energy delivered both by the Thulium laser and the 1470nm diode is predominantly absorbed in water and therefore similar results in laser-tissue effect can be expected.

In this study, we investigate the mechanical, thermal, and acoustic effects of the 1470nm diode laser on stapes in an inner ear model. Since this laser in theory may be a good alternative for stapedotomy and due to its economic advantages, it is of importance to understand its characteristics for this type of surgery. A better insight in the effects might help us to define safety and efficacy of the diode 1470nm laser and settings to use in stapedotomy.

MATERIALS 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 (Figure 1). The same test setup was previously described and used to visualize mechanical, thermal, and acoustic effects with other lasers[9,17]. The inner ear model consisted of a slab of transparent polyacrylamide gel sandwiched between two glass windows. A 3mm deep artificial vestibule was created in the gel, corresponding to the depth of the 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 artificial vestibule with a small central perforation. A stapes footplate (fresh frozen human cadaver) was placed directly on top of the perforation in the dialysis membrane thereby ensuring that the footplate is in direct contact with the fluid without sinking.

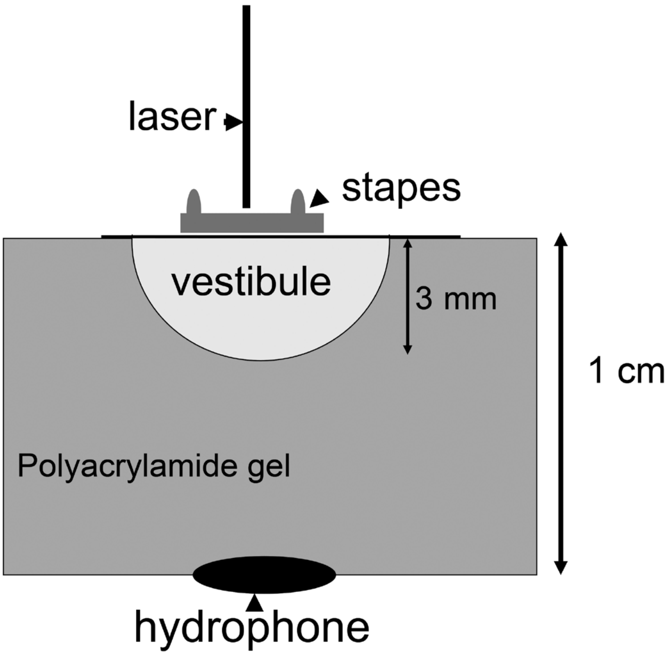

FIGURE 1. inner ear model as seen by the high speed camera. The inner ear model consists of a polyacrylamide gel with an artificial vestibule, a fresh frozen human stapes and a laser fiber. A hydrophone is placed 1cm below the stapes footplate. This model was contained in a glass container and placed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

All tests were conducted at room temperature. The fiber tip of the 1470nm laser was placed directly on the footplate before firing the laser. Three fenestrations were created (no overlapping) on every stapes footplate to confirm reproducibility of the observed effects. For each laser setting, 3 stapes were used to find the optimal setting to make a fenestration. For the analyses of mechanical, thermal, and acoustic effects we used 3 or 4 stapes per experiment. We used a total of 14 stapes.

Laser

The 1470nm diode laser (neoV1470, Haeshel, Israel) was coupled to a 273µm fiber (neoV1470, Haeshel, Israel). During stapes surgery, lasers are used to create a few small perforations in a round fashion (the so called “rosette” technique). These single small perforations together create one big hole in the footplate. When using energy settings with 2W and 2,5W and different pulse time of 50, 75 and 100ms, separate layers of the footplate ablate instead of making a clear hole. A single pulse of 3,0W fired for 100 ms is the lowest possible setting in which a clear perforation can be ensured with a single shot in this experimental setup. The total energy over the irradiated surface (fluence) was 5,16 J/cm^2.

Mechanical Effects

The stapes in the inner ear model with the laser was placed in the imaging setup. Mechanical effects as a result of perforation in the stapes occurred within the first millisecond after the laser pulse. The high-speed camera allowed us to capture processes occurring around the footplate and in the vestibule. High-speed images were made from two viewing angles. Side view images, “perpendicular” to the footplate, were performed to capture the effects under the footplate. The “above” imaging was made with a 20-degree oblique view from the top to visualize the creation of the fenestration and the effects above the stapes. Frame rate up to 2000 frames per second (f/s) could be obtained using a high-intensity white illumination source. The video clips were examined and ranked independently by three authors (SK, TdB and DK) and scored on bubble, particle, and plume formation, and pressure waves.

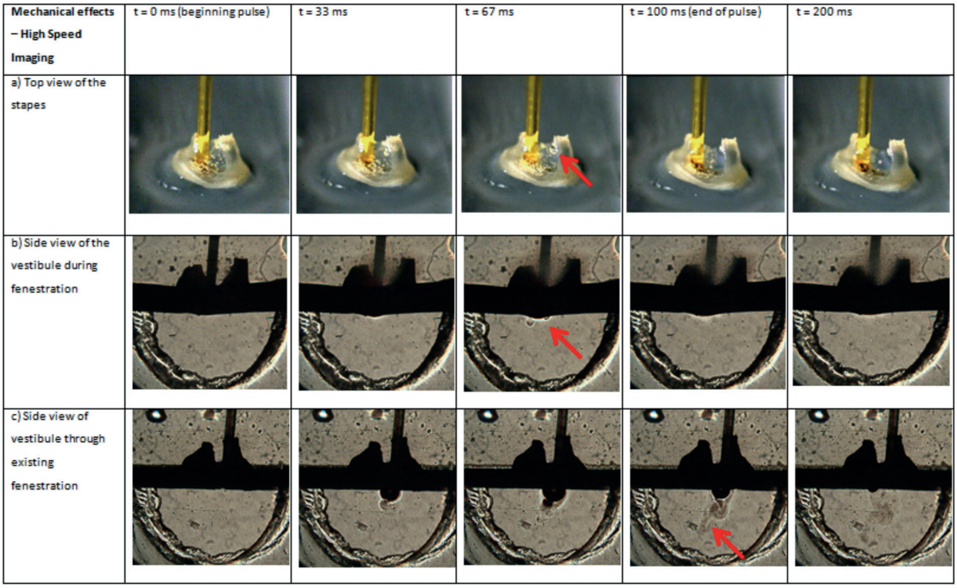

FIGURE 2. Mechanical effects, High Speed Imaging.
Snapshots at t = 0ms (beginning pulse), 33ms, 67ms, 100ms (end of pulse) and 200ms during single shot laser fenestration. Pulse 100ms at 3W.
a) Top view. A plume of gas and small vaporization bubbles arise above the stapes footplate
b) Side view of fenestration. Minimal mechanical effects, one particle. Miniscule gas bubbles push into the vestibule (shown by arrow).
c) Side view when laser hits existing perforation. In the vestibule larger vaporization bubbles, a pressure wave and a small explosion arise.

Thermal Effects

To study the thermal effects, a special optical technique based on color Schlieren imaging was used[18]. This technique visualizes inhomogeneities in the refractive index of a transparent medium induced by a temperature gradient, caused by laser induced heating. Light rays passing through water or a transparent tissue phantom will be deflected. The undeflected and deflected rays are focused on 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. However, these thermal images do not show absolute temperatures but rather the relative local temperature dynamics. Using a high speed camera frame rates up to 2000 f/s were obtained, whereas a standard infrared thermography camera can only detect surface temperatures at a frame rate of 25f/s (at 40ms resolution). The high speed camera enables the visualization of temperature effects inside a physiologic medium like vestibule. This can be combined with a regular high-speed camera at high magnification using standard close-up optics. The video clips were examined and ranked independently by the authors (SK, TdB and DK), after which results were compared. Discrepancies between independent rankers were resolved by discussion, and reported results are based on full consensus.

Acoustic Effects

The sound production was measured using a hydrophone (Pro Signal, Omni, sensitivity -42 ±3dB, maximum frequency range 20kHz, diameter 2,7mm), located 1 cm below the stapes footplate. Recordings were made during 100ms after onset of the laser pulse. The hydrophone was calibrated with a reference source (Blaupunkt speaker, PCxb352) presenting pure tones over the frequency range from 125Hz to 16kHz at 10cm distance from the hydrophone. Sound levels were determined with a sound level meter (Bruël and Kjær, 2203) and a 1 inch microphone (Bruël & Kjær, 4132). For each laser fenestration a 100ms audioclip was recorded, during the 100ms pulse. The data were analyzed using custom-written software in Matlab 7.6 (the Mathworks, Inc) programming environment.

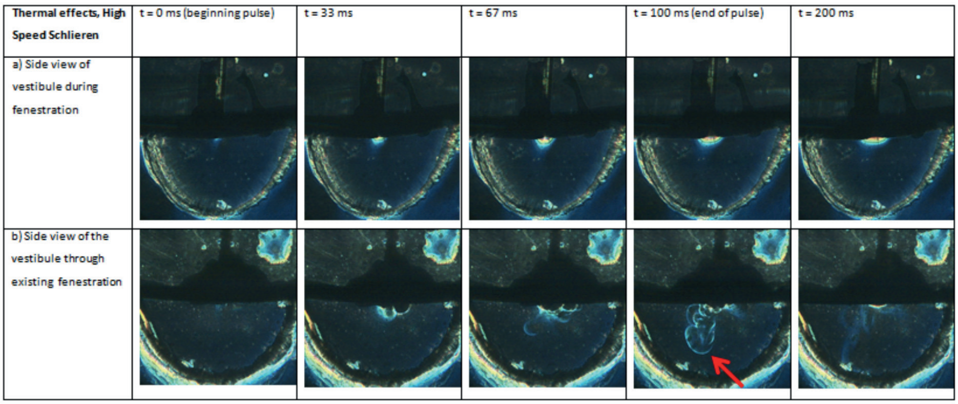

FIGURE 3. Thermal effects, High Speed Schlieren.
Snapshots at t = 0ms (beginning pulse), 33ms, 67ms, 100ms (end of pulse) and 200ms during single shot laser fenestration. Pulse 100ms at 3W.
a) Side view of fenestration. Note superficial heating, yellow, red and blue color rings.
b) Side view when laser hits existing perforation. Note the flow occurs, penetration depth with red arrow.

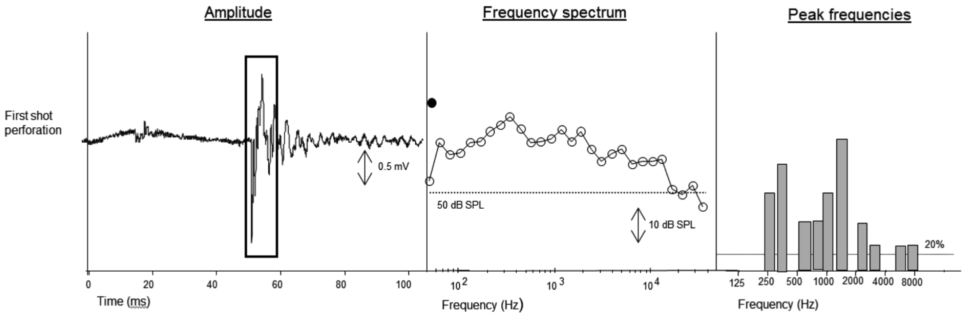

FIGURE 4. Acoustic measurements.
A raw audio recording for the diode 1470nm laser (left to right). Over the time frame of 10ms with largest amplitudes (box), a frequency peak was obtained (reference line of 50 dB SPL). The peak frequencies were shown for all the measurements taken.

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The 10ms with highest amplitudes were analyzed. Over this time frame a Fourier frequency analysis was performed, breaking the signal into 1/3-octave bands. The peak frequency, that is 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. Converting to dB (A) makes it possible to compare the potential harm of the sound produced by different lasers. Ten recordings were performed to ensure reproducibility

RESULTS

Frames of the High-Speed camera are shown in Figure 2 and 3. The laser pulse starts at t=0ms. The figures show single shots at different times during perforation until t=100 ms which represents the end of the laser pulse.

Mechanical Effects

The high temperatures of the laser irradiation of the 1470nm laser in the inner ear model caused dehydration of the stapes bone. This induced a small fenestration in the stapes footplate. During the laser pulse, a plume of gas, and small vaporization bubbles arose above the stapes footplate because of heating a superficial layer of water on the footplate (Figure 2a). Finally, a clear and small perforated conical hole appears with a ring of brown colored carbonized formation.

In the vestibule, 67ms after the start of the laser pulse miniscule gas bubbles pushed into the vestibule (Figure 2b and Video file 1). The bubbles superficially distributed below the stapes footplate due to direct absorption of the energy in the perilymph. These mechanical effects arose during the laser pulse, similar to our findings when using a Thulium laser[9].

When firing a second shot in a fenestration even larger vaporization bubbles, pressure waves, and a small explosion rose below the footplate within 67ms (Figure 2c). The vaporization bubbles stuck together, congregated into one central bubble and penetrated deeper. During these effects a pressure wave occurred. Explosions and implosions were observed and pushed into the depth of the vestibule.

Thermal Effects

On the side view of the inner ear model thermal imaging visualized high temperature underneath the stapes footplate (Figure 3a). We observed different colored rings representing a high temperature gradient. This excessive heat distributed in a 0,5 mm zone of the vestibule. As mentioned earlier, using the color Schlieren technique it is not possible to show absolute temperatures. It takes more than 100ms until the perilymph has cooled down.

A second laser pulse translocated bubbles and pressure with a typical heating pattern with colored temperature rings around the vaporization bubbles (Figure 3b and Video file 4). This increased temperature around the vaporized bubbles which also translocated in the depth of the vestibule. Perilymph locally heats up around the bubbles.

Acoustic Effects

The sound measured was generated by the laser pulse during perforation. The raw recordings showed that the diode 1470nm laser produced peaks during 40-60ms of the interval. Analysis of the sound production laser pulse were calculated over the 10 ms with highest amplitude (Figure 4). Peak amplitudes are correlated to the moments that the vaporization bubbles arise and explode in the vestibule. This laser system generated noise with a frequency range peaking around 500-1500Hz and maximally reaches 93 ± 8dB (A). Background noise generated by formation of the perforation in the bone is not detected by the hydrophone and is therefore considered minimal.

DISCUSSION

The diode laser with wavelengths of 1470nm is capable of creating a hole in the footplate to make a fenestration in the stapes. However, caution is appropriate since we found thermal and mechanical side effects during experiments in our inner ear model. These effects are potentially harmful to the inner ear function and this is related to induction of vertigo, tinnitus, and hearing loss.

It remains unclear to what extent thermal, mechanical and acoustic effects can cause damage to the inner ear function, because we do not know the cutoff point that results in damage. Previous research showed that the mechanical and thermal effects seen in the inner ear, varied enormously between lasers[9,17]. It seems logical to assume that the laser showing least side effects, is the safest to use in stapedotomy. Using the same setup as in our previous work with KTP, 980nm diode, Thulium and CO_2 lasers, allows us to compare these different types of lasers.
As we know, lasers in the infrared spectrum (like the Thulium and CO_2 laser) are well absorbed in water. These lasers seem to make more vapor bubbles which cause more noise, compared to KTP laser. Infrared lasers have small differences which we did not discriminate in previous studies. The KTP laser has different laser-tissue interactions include low water absorption coefficient and less mechanical and acoustic effects. However, we wanted to get better insight into the effects and characteristics of the 1470nm laser due to define safety and efficacy of the laser and settings to use in stapedotomy.

Where does this 1470nm laser stand? The first pulse to make a perforation in the footplate seems to be rather safe. When making a close or overlapping perforation, as in clinical use with the so called "rosette technique", larger effects in the vestibule are seen. The excessive energy penetrates into the vestibule and is absorbed in the perilymph directly causing vapor bubbles, pressure waves, and heat. These effects could be damage the inner ear. The diode 1470nm is predominantly absorbed in water, showing a combination of bubbles, pressure waves, and therefore a deeper penetration of heat whose effects could be damage the inner ear[17]. During stapes surgery, most surgeons make a few small perforations in a round fashion on the stapes footplate. Using this rosette technique, close perforations will overlap and firing a laser pulse in an existing perforation will occur. Making more than one fenestration on the stapes footplate will increase the risk of mechanical, acoustic, and mechanical effects, causing possible harm. These effects were not seen when using a KTP or 980 nm diode [9,17].

The magnitude of the bubble formation and the matching pressure waves in the sound recordings, are different to the effects seen with the other lasers. The Thulium laser shows this effect as well. We interpret these findings as follows. In our inner ear model, the borders of the vestibule are made out of gel which is partly flexible. It is known that in closed spaces, bubble formation is less likely. The bony wall surrounding the vestibule cannot expand, and therefore bubbles might be smaller than we see in our inner ear model[19]. In other words, we might have overestimated this bubble formation. On the other hand, the flexible boundaries of the vestibule in our model might dampen the pressure waves occurring during the bubble formation. As a result, we might underestimate the power of these pressure waves.
The intra operative sound production of the laser influences possible damage in the inner ear. Animal research has shown that a temporary threshold shift can occur with impulse noises over 110dB[20]. In humans impulse noises differs between individuals and there appears to be a large diversity in individual sensitivity[21]. Therefore, the impulse noise of this 1470nm laser seems to be small and irrelevant.
Clinically, the occurrence of mechanical effects as fast pressure differences in the inner ear could be potentially damage hair cell functioning. Animal studies supports this finding[4,6,22,23]. The diode 1470nm laser has not tested in animals yet.

Nowadays, there is a large diversity in using lasers in stapes surgery. We evaluated that the diode 1470nm has a relatively high absorption in water or perilymph. But as long as we do not know the possible damage the side effects could give in clinical setting, it seems advisable to use the laser with the least potential harm. KTP and 980nm diode are known safe alternatives to use for stapes surgery. As the diode 1470nm laser has a relatively high absorption in water, this laser is more suitable for soft tissue surgery. Clinical and animal studies need to be undertaken to verify all benefits.

CONCLUSION

The 1470nm diode laser shows large mechanical, acoustic, and thermal effects in our inner ear model for stapes surgery. This is due to the high absorption of the wavelength in water followed by bubble formation in the inner ear. We would not advise surgeons to use this laser due to the risk involved that we found and published earlier.

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6

CAPTURING THERMAL, MECHANICAL AND ACOUSTIC EFFECTS OF THE DIODE (980NM) LASER IN STAPEDOTOMY

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ABSTRACT

Introduction

The Diode laser, with a wavelength of 980nm, 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 (= 250μs 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 100ms, 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 980nm 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.

Keywords

Otosclerosis, Laser, Stapedotomy, Diode, Trauma, Hearing

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 (488nm) and KTP (532nm) 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 (2940nm) 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 (10600nm), 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 1064nm 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 980nm 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 980nm, 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 3mm 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

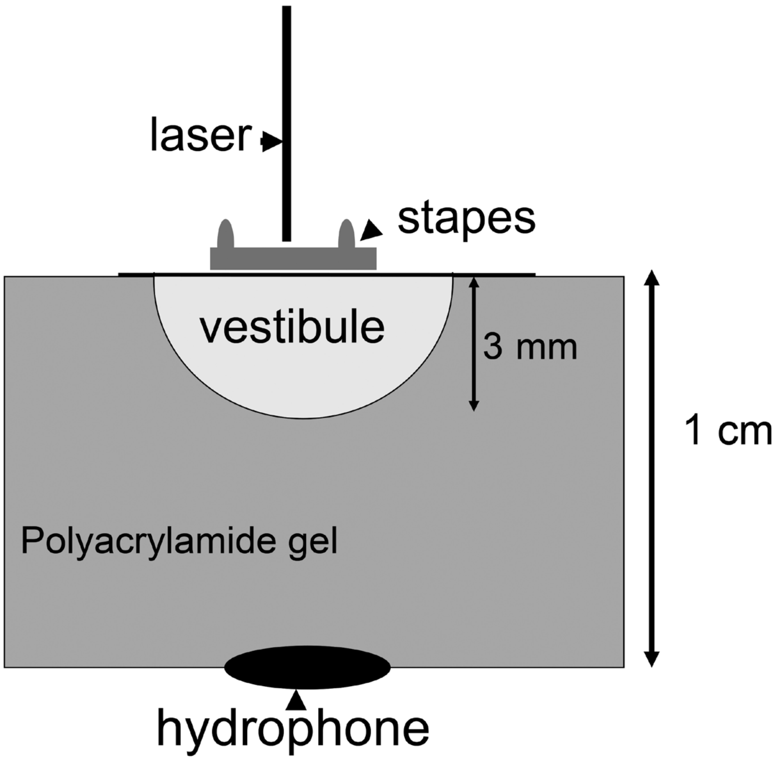

FIGURE 1. inner ear model as seen by the high speed camera. The inner ear model consists of a polyacrylamide gel with an artificial vestibule, a fresh frozen human stapes and a laser fiber. A hydrophone is placed 1cm below the stapes footplate. This model was contained in a glass container and placed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

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.

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) (= 250µs 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 1000f/s (at 1ms resolution) were obtained. In contrast: a 'standard' thermal camera can only typically detect surface temperatures at a frame rate of 25f/s (at 40ms 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 6mm), which was placed 1 cm below the stapes footplate.

Recordings were made during 100ms 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 (125Hz – 16kHz) at 10cm 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 10ms 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 532nm KTP laser (IDAS, Quantel Derma, Erlangen, Germany), a 2μm continuous wave ('Thulium') laser (LISA laser, Katlenburg, Germany) and a 10.6μm continuous wave CO_2 laser (A.R.C. laser, Nurnberg, Germany) were already tested. Settings were conform clinical practice; KTP 1W, 100ms, fiber 200 micron; Thulium 5W, 100ms, 372 micron fiber; CO_2 2W, 100ms, 250nm hollow wave guide. A flow with Helium gas was delivered through the center of the hollow wave fiber (> 1bar) 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, 8mm 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 980nm hand-held, battery-driven Diode laser, with a 200µm fiber (FOX, A.R.C. Laser Nurnberg, Germany) was used. A single-pulse laser beam of 3.0W 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, 100ms, 5 pulses.

RESULTS

Mechanical effects

The 980nm 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) 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 see Supplemental Digital Content 2).

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 Supplemental Digital Content 3). 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).

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). 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). 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).

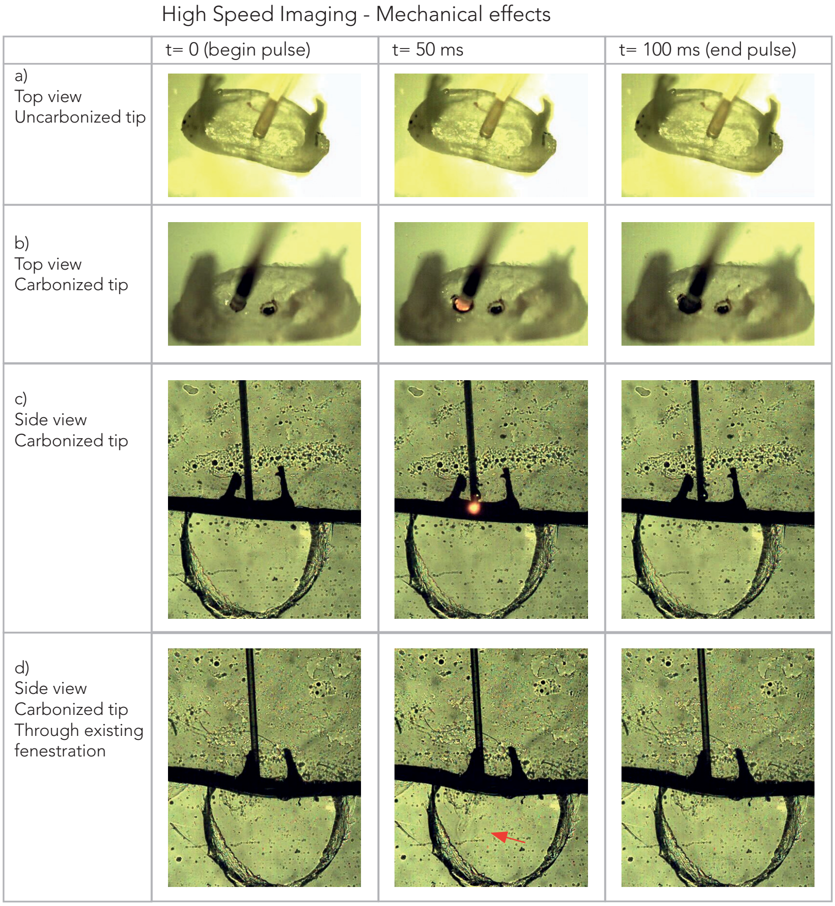

FIGURE 2. Mechanical effects. High speed Imaging. Snapshots at t=0, 50ms, and 100ms, during single shot laser fenestration. Pulse 100ms at 5W
a) Top view, no carbonization of tip, no effects on footplate.
b) Top view, carbonization of tip. Small fenestration with thick carbonized rim
c) Side view, carbonized tip. Heating of tip. No mechanical effects
d) Side view, carbonized tip, through existing fenestration. In the vestibule a flow occurs (red arrow).

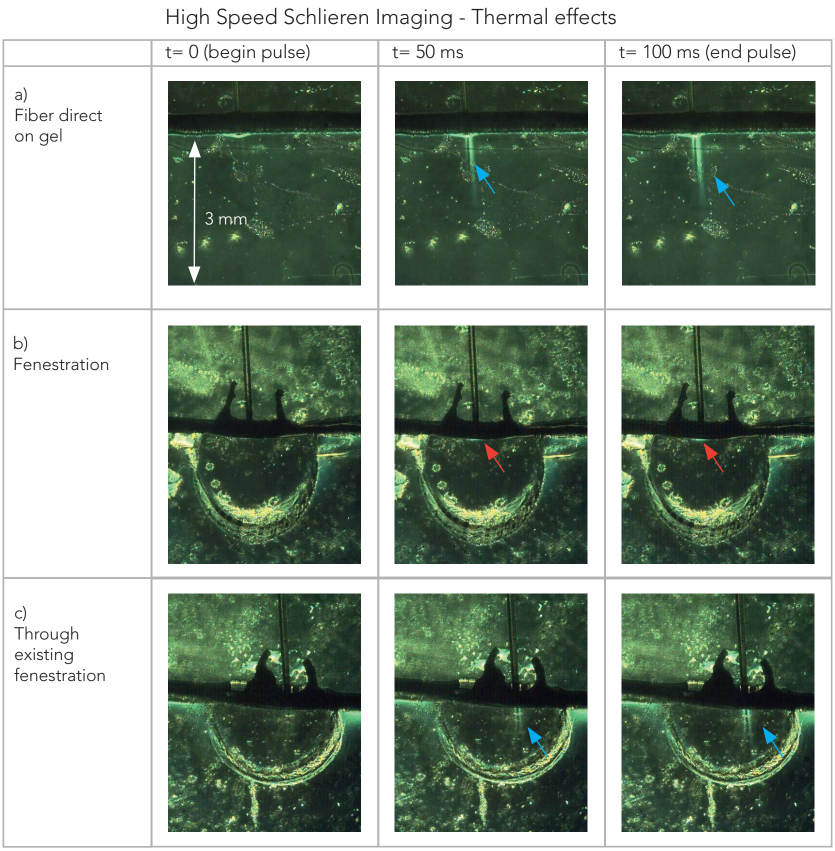

FIGURE 3. Thermal effects, High Speed Schlieren. Snapshots at t=0, 50ms, and 100ms, during single shot laser fenestration. Pulse 100ms at 5W
a) Fiber direct at gel. Note the penetration depth, blue arrow.
b) Side view of fenestration, with carbonized tip. Note only superficial heating, red arrow.
c) Side view when laser hits existing perforation. Note the penetration depth, blue arrow

Acoustic effects

The Diode laser generated limited noise. Fourier analyses showed that the Diode laser generated mostly low-frequency sounds, around 100-150Hz. The total loudness of the noise produced during the 100ms 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 150Hz (**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.

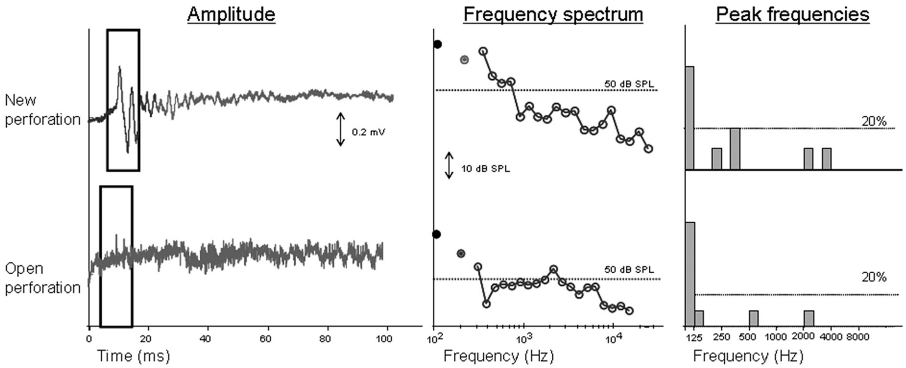

FIGURE 4. Acoustic measurements.
Two raw audio recordings are shown; one when making a new perforation (top), one when firing through an existing perforation (bottom). Over the time frame of 10ms with largest amplitudes (box), a frequency spectrum was obtained. This frequency spectrum is shown with a reference line of 50dB 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.

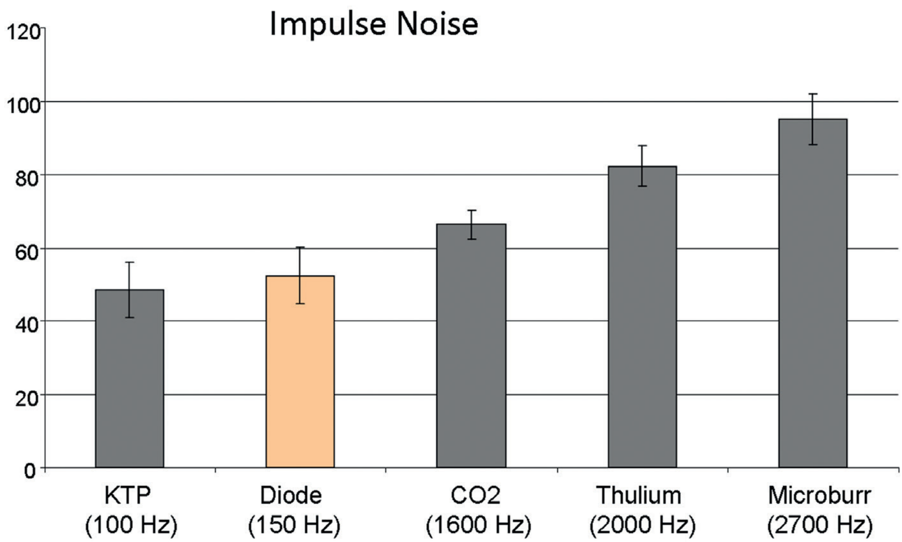

FIGURE 5. Comparison of the impulse noise generated by the Diode Laser, compared to other lasers and drill. The peak frequency of the noise is shown between brackets

DISCUSSION

In this study, special imaging techniques were applied to visualize mechanical and thermal effects during stapedotomy using the Diode (980nm) 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 980nm wavelength penetrates the vestibule. However, absorption of the 980nm 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 2940nm 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 980nm Diode laser is low in all frequencies and therefore neglectable as a source of SNHL.

Overall, in our setup the 980nm 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 (980nm) 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

TECHNICAL NOTE:

A novel handpiece for open laser surgery with integrated surgical smoke evacuation

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Submitted

ABSTRACT

The use of laser surgery is widely accepted. Laser systems are becoming cheaper and more attractive to use as an energy delivery device. However, smoke induced by laser surgery is potentially hazardous and the development of laser fiber handpieces for open surgery has never been given priority by the industry. Also, surgical smoke impedes the view on the surgical plane.

A prototype of an innovative ergonomic laser fiber handpiece with integrated surgical smoke evacuation and a dynamic fiber extension cannula was made.

This device can contribute extensively in a better air quality during open laser surgery compared to open laser surgery without smoke evacuation. The efficient smoke evacuation modality at the source of the ablation zone will also improve visibility during open laser surgery. Also, improved ergonomics contributes to better control and handling of the laser fiber during open laser surgery.

INTRODUCTION

Laser surgery has obtained an established role in the operating theatre[1] . Especially in urology and in the ear nose and throat (ENT) specialty[2,3]. Most lasers deliver their energy through a thin (less than a mm) silica fiber and are therefore very suitable for endoscopic surgery.

Laser surgery for "open" (not endoscopically) surgery is still upcoming. In the fields of urology, ENT, gynaecology, and thoracic surgery an increasing number of clinical trials are performed to explore the advantages of open laser surgery[4–7]. The benefits of laser surgery compared to electrosurgery are very prominent when resecting a tumor in muscle tissue such as the tongue[5]. Electrosurgical resection of muscle tissue, results in contracting tissue due to direct electrical stimulation of the muscle, however with the use of laser surgery, muscle contraction is absent[5]. This contributes to a controlled surgical plane when resecting parts of the tongue.

In the University Medical Center Utrecht (UMCU) the Thulium laser is used in different specialties. The ENT department uses this fiber guided laser extensively for the resection of intra oral tumors. Standard commercially available laser fiber handpieces are used. These handpieces are resterilizable instruments with several replaceable tips. The laser fiber is fixated by friction due to a small compressed silicon tubing (figure 1D). There are several drawbacks to these instruments. First, the difficulty in cleaning due to the small space inside i.e. tissue and char remains. Second, the silicone tubing is often flushed away during the cleaning process, and has to be replaced by an employer of the sterilization department or by a surgical nurse. Third, multiple devices are needed in stock when more than one procedure is planned per day and potentially creating logistic problems with availability due to cleaning and re-sterilizing process of the resterilizable instruments. A single use disposable instrument would solve these problems.

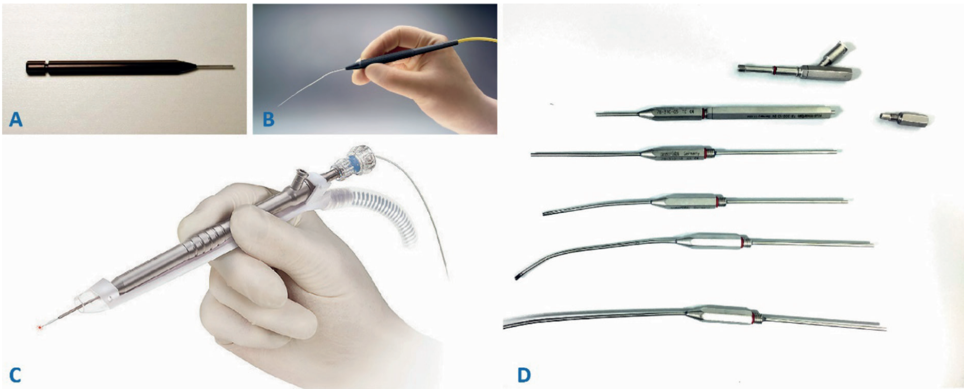

FIGURE 1. Variety of laser fiber handpieces. A: Simple reusable handpiece with screw fixation at the left (TTI Medical, San Ramon, USA) B: Single use handpiece in which the laser fiber is fixated in the device (Iridex, Mountain View, USA) C: Reusable laser fiber handpiece with single use clip-on smoke evacuation tubing (KLS Martin Group, Tuttlingen, Germany). D: ENTLas reusable handpiece (Lisa laser, Katlenburg-Lindau, Germany). This set has 5 exchangeable straight tips (5 to 23 cm in length, which have been bend during use. Note the small parts that can be easily lost in the cleaning and sterilization process.

Energy delivery devices which are used for the resection of tissue, often create surgical smoke[8,9]. Surgical smoke decreases visibility in the surgical field and contains many toxic components[10]. Also, surgical smoke can contain vital viral parts which can be potentially infectious when inhaled[11]. Users of energy delivery devices increasingly use smoke evacuation systems for extracting these toxic components from the environment[12]. Smoke evacuation equipment often consists of a standalone air suction device or a vacuum wall socket. This equipment is coupled to sterile tubing that is directed to the operating field. Subsequently the tubing can be held by an assistant or coupled directly to an energy delivery device. Direct coupling of the tubing to the energy delivery device is preferred. In this way, the suction device is always close to the resection plane where the smoke is created, and the smoke evacuation is not dependent of on the skills of an assistant. This creates a clearer surgical field without extra “hands” in the surgical field.

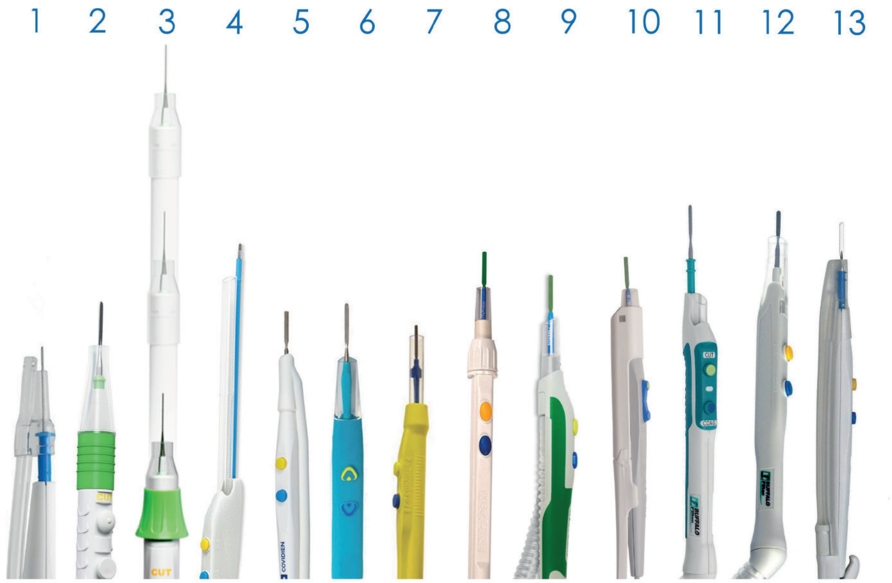

FIGURE 2. Electrosurgery handpieces with integrated smoke evacuation. Note that most of the devices do not have a dynamic length adjustment of the active electrode.

In electrosurgical equipment, there are many different kinds of electrosurgical pencils available with smoke evacuation tubing directly attached. The choice in laser fiber handpieces with directly coupled smoke evacuation tubing is very limited.

The aim of this study was to develop a prototype laser fiber handpiece with enhanced ergonomics and an integrated smoke evacuation modality.

TABLE 1. Electrosurgical handpieces with integrated smoke evacuation pictured in figure 2.

Brand	Name	Type
1.Surgiform	*SAF-T-VAC*	*Clipped –on tubing*
2.SafeAir	*SafeAir Smoke pencil*	*All-in-one*
3.SafeAir	*SafeAir Telescopic Smoke Pencil*	*All-in-one*
4.Covidien	*Valleylab Smoke Evacuator*	*All-in-one*
5.Covidien	*Accuvac*	*Clipped-on tubing*
6.Cimpax	*C-VAC Tornado*	*All-in-one*
7.ConMed	*GoldVac*	*All-in-one*
8.Megadyne	*Telescopic Sm. Evac.*	*All-in-one*
9.Megadyne	*ZIP Pen*	*All-in-one*
10.Megadyne	*ATTACHA VAC*	*Clipped-on tubing*
11.BuffaloFilter	*PlumePen Elite*	*All-in-one*
12.BuffaloFilter	*PlumePen Pro*	*All-in-one*
13.BuffaloFilter	*PlumePen Adapt*	*Clipped-on tubing*

METHODS

Current market

The current market was explored for existing handpieces for open laser surgery (Figure 1).

Improvement

Shortcomings of the current handpiece were investigated by interviewing ENT surgeons who used the Thulium laser regularly for intra oral surgery. This resulted in a list of requirements for the laser fiber handpiece (table 2).

TABLE 2. Requirements of the laser fiber handpiece obtained from user interviews

Handling the laser fiber
The laser handpiece must securely fix the tip of the laser fiber in relation to the hand.
The laser handpiece shall enable an adjustment of 60 to 160mm from the tip of the fiber to the hand. The cannula must not move during use of the handpiece.
The cannula must not rotate during use of the handpiece. *The fiber must stay at the same position during normal use of the handpiece.*
Smoke evacuation
Removal of the smoke must be performed by suction through standard smoke evacuation tubing, connected to the handpiece.
The smoke evacuation tube should not hinder the user in their handling of the fiber and handpiece.
Mechanical interface
The handpiece must be able to fit both 273µm and 365µm laser fiber.
The handpiece must enable fixating the fiber without damaging it.

Available technologies

Handpieces with integrated smoke evacuation for electrosurgery were explored as these devices have similarities in both ergonomics and applications (table 2 and figure 2).

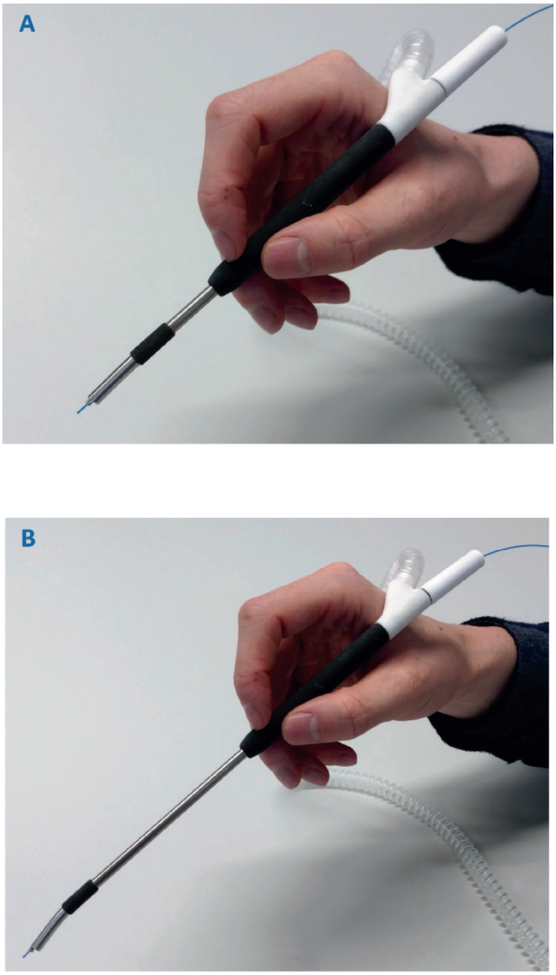

FIGURE 3. A: Prototype with the cannula pushed in the handpiece. **B:** Prototype with the cannula pushed out. The length of the metal cannula is dynamic and adjustable from 60 to 160mm from hand to laser fiber tip. Note the smoke evacuation tubing at the back of the hand. The fixation point of the tubing can rotate 360° in order to position the tubing in the most convenient way.

Prototype
From the requirements, a design was developed in SOLIDWORKS and subsequently printed in part with selective laser sintering in nylon and in part with an Objet Connex500 3d printer with a polymer for the base and an elastomer for the grip areas (figure 3). The shaft consists of steel modified steel tubes. Due to intellectual property, the inner design of the prototype is not disclosed.

In Vitro testing
For the functional smoke evacuation test of the prototype a Thulium laser (Revolix Junior, Lisa Laser, Katlenburg-Lindau, Germany) with a bare single use laser fiber (365 μm, Lisa Laser, Katlenburg-Lindau, Germany) was used. The laser fiber was positioned into the 3d printed prototype, with the laser fiber tip protruding from the nozzle of the prototype. The prototype laser fiber handpiece was connected to a stand-alone smoke evacuation device (Buffalo silent whisper turbo, Buffalo NY, USA). The handpiece was positioned above a homogenous piece of meat which was moving at a constant speed of 5,4mm/s on a linear actuator. The tip of the laser fiber was in contact with the meat. The cannula of the smoke evacuation was approximately 3 to 4mm removed from the tip of the laser fiber. The Thulium laser was set at 10W continuous wave (CW) and video captures were made with a high-speed camera (Mini UX50, Photron, Tokyo, Japan) at frame rate of 60fps. A stroboscope (X-Strobe X1200 PerkinElmer, Bridgeville, PA, United States) was triggered by the high-speed camera to create a forward-light illumination. The forward-light illumination enhanced the visibility of the smoke by forward scattering of the light into the camera (figure 4). The video recordings were evaluated for visual presence or absence of laser smoke (figure 5).

RESULTS

Current market
The current market offers a small variety of laser handpieces. There is little variety in design and functionality. Almost all commercial handpieces are simple products that are designed for grasping the fiber and making it possible for the surgeon to control the laser fiber during surgery. Only handpiece C in figure 1 has a clip-on system which is connected to smoke evacuation tubing. Handpiece set D has been purposefully bent during use in the (operating room) O.R. by the surgeon. This emphasized the need for a curve in the distal end of the handpiece in order to treat areas that are difficult to reach with a straight instrument.

Parallel technologies

In the field of electrosurgery many handpieces are available. A list of the most common devices is shown in table 2 and in figure 2.

Improvements

A list of requirements is shown in table 1, and the new prototype is considered a redesign of the currently used handpiece. The list of requirements is a guideline for designing the laser handpiece.

Prototype

The prototype that is constructed is shown in figure 3. Standard smoke evacuation tubing fits on the handpiece. The tip of the laser fiber is slightly protruding from the cannula in which the electrosurgical smoke is evacuated. The metal cannula is easily extendable by simply pulling the cannula out. Since the fiber is fixated on the extendable part, the fiber does not need manual repositioning. Also, the metal cannula is fully rotatable for easy reposition of the laser fiber in difficult to reach areas.

In vitro testing

The video recordings show the difference between the smoke evacuation off and 50% capacity on. Snap shots were taken during laser vaporization with the laser fiber in contact with the homogenous meat (fig. 5).

The new laser fiber handpiece has four main advantages over conventional laser fiber handpieces.

First, the device has integrated smoke evacuation which reduces the amount of toxic and microbiological (viral parts) components in the air very effectively. As the smoke evacuation is located very closely to the smoke source almost all smoke particles are transported into the smoke evacuator. Especially in narrow working places as the oral cavity, the surgical view increase when using the new laser handpiece. Surgical smoke is directly removed and there is no smokescreen blocking the view.
Second, the need for an extra hand and tubing is redundant, which enables a better view for the surgeon

Third, the cannula is a dynamic extendable tube that facilitates a flexible working area. For changing the length of the device, it is not necessary to change parts of the handpiece, which saves valuable time and enables flexibility.

Fourth, the device is designed in regards to ergonomic design. The handling of the handpiece is an important issue.

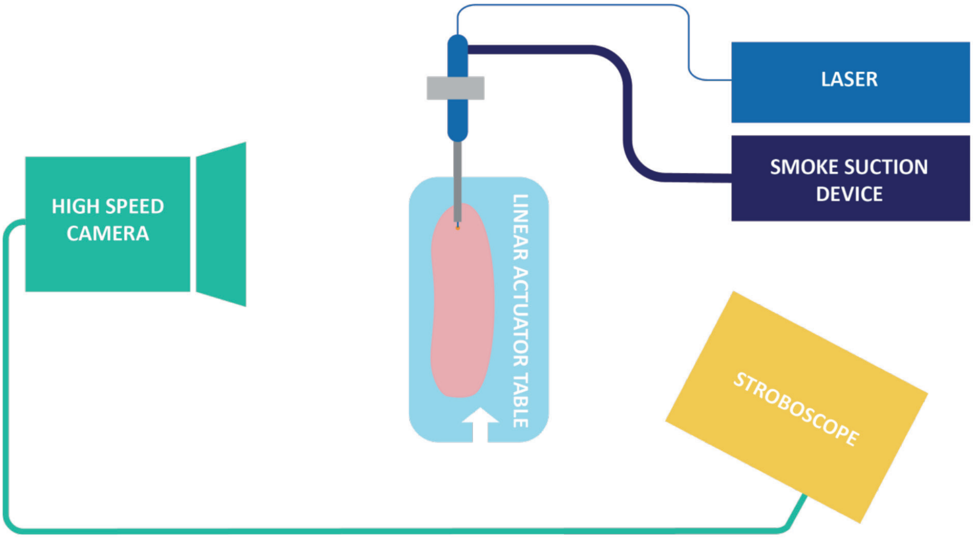

FIGURE 4. The forward scatter illumination setup seen from above. The high-speed camera captures the forward scattering light of the surgical smoke.

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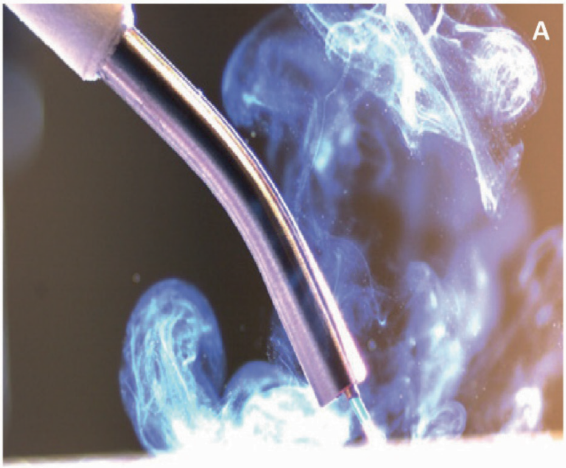

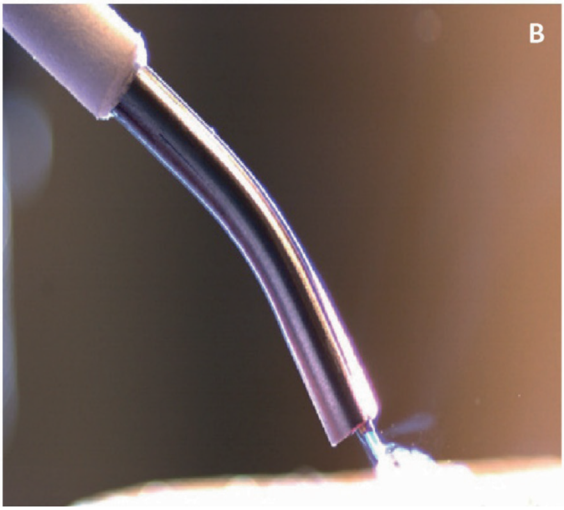

FIGURE 5. A. Distal end of the cannula of the handpiece, while laser is in use with the smoke evacuator turned off. The surgical smoke is clearly visible in the blue scattering light from the stroboscope. **B.** Distal end of the cannula, while laser is in use and the smoke evacuator is turned on at 50% of its capacity. The surgical smoke is visually evacuated.

DISCUSSION

This novel laser fiber handpiece is an instrument that facilitates a smoke free OR with strongly improved ergonomics. The need for smoke evacuation is necessary as the smoke contains over 62 toxic and biochemical components[13]. A basic study on surgical smoke found that ablating 1g of tissue by a CO_2 laser contains the smoke of three unfiltered cigarettes[12]. As we proceed to a tobacco smoke free environment it is obvious that surgical smoke should also be reduced as much as possible. This is very important as the OR staff should not be exposed to surgical smoke due to toxic components and viral components[14].

Future design iterations will incorporate the possibility for the use of hollow wave guide CO_2 laser fibers.

The final clinical handpiece will be a single use device. The handpiece will be completely mounted when taken out from the packaging. This will diminish the risk of losing parts perioperatively. Also, as it is a disposable device there is no need for the OR or sterilization department to assemble and disassemble the handpiece. The overall handling time decreases and the efficiency increases. The laser fiber handpiece is designed as a single use instrument, which decreases the risk of residual contamination after the cleaning and resterilization process. Also, the number of procedures a day is not limited due to cleaning and sterilization time

CONCLUSIONS

A new laser fiber handpiece with integrated surgical smoke evacuation has been designed and tested in an *in vitro* setup. A clinical device will be developed with sebsequent testing. This handpiece will contribute to a better surgical handling, view and less polluted air in the OR with open laser surgery.

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8

GENERAL DISCUSSION

GENERAL DISCUSSION

The choice of the optimal energy device for deployment in a particular field of surgery is a challenge. Lasers have several advantages over electrosurgery, but there are lasers operating at many different wavelengths with complicated user-interfaces to operate (and brands to choose from). Understanding the mechanisms of light-tissue interactions should be the basis for making the right choice, as described in the introduction. In this thesis, a variety of infrared lasers have been investigated *in vitro* and *ex/in vivo*. The infrared region for clinical lasers is very interesting as it is a wide region (810nm-10.600 nm) with many kinds of laser tissue interaction and clinical applications. It is concluded that various wavelengths can be used for specific clinical applications depending on the laser settings. For example, as described in chapter 3, the 810nm laser and 1064nm laser could be replaced by the Thulium laser. Originally, the 810nm laser and the 1064nm laser were safely used to make a fenestration by vaporization in a thin membrane in the brain. This was only possible by coating the fiber tip with a thin carbon layer to enhance absorption of the laser light ('black' tip). This coating was not necessary anymore with the introduction of the Thulium laser due to direct absorption of the light in soft tissue (water) with a reproducible tissue effect.

Chapter 3, 5 and 6 describe the effects of laser irradiation with in *vitro* set ups. The 980 nm, 1470nm diode lasers and the 2013nm Thulium laser are studied for various clinical applications. Chapter 3 describes the thermal effects for a neurosurgical procedure. Chapters 5 and 6 describe the thermal and acoustic effects simulating stapedotomy in an inner ear model. For both applications, the color Schlieren technique was used to study thermal effects in a qualitative way. This technique provides a good insight in the thermo dynamic processes for understanding the basic physical characteristics.

In chapter 3, the heat penetration of the Thulium laser was studied using a special setup mimicking the environment of the floor of the third ventricle. With all tested laser parameters, a fenestration is achieved in the tissue model. By visualization of the thermal effects, it was shown that the heat penetration beneath the phantom, representing the floor of the third ventricle, is very small for the power settings of 1.0W and 2.0W. At higher power settings (4.0 and 7.0W), the heat penetration increases. At 7.0W explosive vapor bubbles are formed inducing turbulent, hot water jets, which can reach a depth of 6.0mm. Translating this data to the clinical situation, the probability of accidental heating of surrounding tissues increases at higher power settings. In contrast, for settings below 2.0W, the Thulium laser irradiation stays close to the fiber tip, preventing damage to the surrounding tissue while still effective in perforation. The *in vitro* study, is very helpful to the determine the optimal laser setting for the clinical situation and the degree of the thermal side effects to surrounding tissues. An important observation was the formation of turbulent hot water jets above the threshold where water vapour bubbles are formed (7.0W) which extend the thermal effects from just a few mm to over 6mm. Our clinical data from over 100 patients shows that Thulium LA-ETV is effective and safe. All had a successful fenestration with laser setting below 3.0W. There was no evidence of thermal injury to the basilar artery in any of the patients. The clinical data confirmed the in *vitro* observation that an effective fenestration could be obtained safely with laser powers below 3.0W.

The *in vitro* experiment has aspects that are different compared to the clinical situation. Gelatin was used as tissue phantom. It does not have the mechanical strength, however, it can provide reproducible results to study the thermal effects. Due to flushing with a Ringer's lactate solution *in vivo*, there is an additional cooling effect. Gelatin has the advantage of containing a high protein content.[1] Other tissue models have been tried like chicken-skin and real cadaver material, but all materials had the disadvantage of not being reproducible and therefore strongly influencing the outcome of the results.

The flexible laser fiber and good reproducibility of the thermal effect make the Thulium laser an attractive instrument for LA-ETV. The Thulium laser creates an opening by vaporization of the obstructing tissue. Compared to the mechanical technique in ETV, the Thulium laser could have the hypothetical advantage of a vaporizing laser in general compared to for example balloon dilatation. Vaporizing the floor of the third ventricle would create a more patent fenestration instead of stretching the tissue by a dilating balloon.

Chapter 5 and 6 describe the basic physics of thermal distribution in two *in vitro* studies with an inner ear model, for laser stapedotomy surgery. The 980nm and the 1470nm diode lasers were used. The Thulium laser was not included because clinical results and other *in vitro* experiments already proved that the Thulium laser has unwanted side effects for the use in stapedotomies[2]. It is assumed that damage to the inner ear during stapes surgery 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[3,4]. The 980nm laser and a 1470nm diode laser are both capable of creating a fenestration of the footplate of the stapes. The fiber tips were all pre-carbonized on a wooden spatula before use. These two lasers were studied

separately for the thermal and acoustic effects. In these studies, fresh frozen human cadaver stapes were used in order to have the most natural circumstances. Stapes fixated on formaldehyde might give artefacts as the normal tissue fluids are replaced by formaldehyde, but this is unproven.
The acoustic and thermal effects beneath the stapes caused by the 980nm diode laser were minimal. Correlation to the lasers in previous work, shows the same amount of heating as was seen in the KTP laser, around 4 degrees Celsius[5]. Carbonization of the tip is necessary for preventing transmission of the laser light through the footplate of the stapes and 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. This is an uncontrolled action and has strong effects on the fluence.
While the bone is ablated, some of the heat is transferred to the vestibule. When the same spot is hit twice, the 980nm wavelength penetrates the vestibule. However, absorption of the 980nm wavelength in the perilymph is limited. Nonetheless, as with all lasers that are characterized by limited absorption in aqueous solutions, the 980 nm diode laser could theoretically damage the well-pigmented cells of the neuro-endothelium. 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.
Overall, in our setup, the 980nm diode laser with a blackened fiber tip 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. To prevent unwanted transmission of laser light through the vestibule it might be a good idea to use a laser which has much absorption in water, like the 1470nm diode laser. Theoretically, most of the energy will be absorbed close to the fiber tip and the fluid filled vestibule would function as a "beam stop". The 1470nm diode laser is also capable of creating a hole in the footplate to make a fenestration in the stapes, with similar effects as the Thulium laser (vapour bubbles in the vestibule). However, caution is appropriate since we found thermal and mechanical side effects during experiments in our inner ear model as a result from vapour bubble formation. These effects are potentially harmful to inner ear function and this is related to induction of vertigo, tinnitus, and hearing loss. However, it remains unclear to what extent thermal, mechanical and acoustic effects can cause damage to inner ear function, because we do not know the cut-off point that results in damage.

Nowadays, there is a large diversity in using lasers in stapes surgery. We evaluated that the diode 1470nm has a relatively high absorption in water or perilymph. But as long as we do not know the possible damage the side effects could give in clinical setting, it seems advisable to use the laser with the least potential harm. KTP and 980 nm diode lasers are known as safe alternatives to use for stapes surgery. The pre-carbonized fibers tips are effective for ablating through the stapes bone without causing vapour bubbles in the vestibule[6]. More in general, concluding from these *in vitro* studies and previous studies it is not advisable to use a laser which produces relatively high sound levels and explosive vapour bubble formation in the vestibule, like the 1470nm diode, the Thulium laser and the CO_2 laser[6,7]. It would be interesting to investigate the 1470nm diode laser for soft tissue resections. The 1470nm laser also has high absorption in water, however a factor 10 less than the Thulium laser. No research has been performed in direct comparison of the Thulium laser and the 1470nm laser for open soft tissue surgery. Future studies are needed to determine if the 1470nm laser also functions a good soft tissue cutter, despite the lower energy absorption in water. However, the exact differences between the 1470nm diode laser and the Thulium laser have to be studied, before the 1470nm diode laser can be used safely for Thulium laser applications. The first step would be an *in vitro* thermographic comparison to define the thermal properties. Secondly, *ex vivo* studies have to be designed to compare ablation zones in resected soft tissue specimens between the 1470nm diode laser and the Thulium laser.

In Chapter 4 the feasibility of intra ductal laser treatment for intraductal papillomas causing pathologic nipple discharge (PND) was studied. Lesion extraction with the "basket device" can inherently not always achieve complete removal of the lesion and is restricted to a selected group of polypoid lesions. Laser ablation would be a good treatment for removing the remains of the polyp. Although the procedure has been suggested previously[8,9], data on laser ductoscopy were not reported before.

The main advantage of ductoscopy for localization and treatment of intraductal neoplasms is the reduction of the need for surgery for a benign cause. Before this novel minimally invasive treatment strategy can be implemented in a routine clinical manner, it is important that the benign nature of the intraductal lesion causing the symptoms can be reliably assessed. The basket device is useful for tissue diagnosis in polypoid lesions, with successful (partial or complete) removal in 63-79% of attempts [8,10]. For superficial epithelial lesions or small or obstructing polypoid lesions, basket extraction is not feasible[8,11,12]. For ductoscopic diagnosis and assessment of suitability for laser ablation therefore a commercially available device to facilitate adequate intraductal biopsy and subsequent diagnosis is essential. Diagnostic accuracy may also

be improved with advanced imaging techniques such optical coherence tomography [12,13] or autofluorescence.[13–15]
To treat benign symptoms of PND ductoscopic diagnosis and intervention with basket extraction and/or subsequent laser ablation provides a potential promising minimally invasive approach. Also for symptomatic selective treatment of affected ducts laser ductoscopy may be of use; the use of higher power levels caused shrinkage and thereby complete occlusion of the main duct. A potential future application may be the complete ablation of the ductal epithelium or ablation of precursor lesions as a form of primary prevention of breast cancer. The side branches of the central duct do not rapidly decrease in diameter and is not a limitation when proceeding deeper into the breast.

Chapter 7 describes a novel laser fiber handpiece. Laser fibers are very thin (spring like) with a strong torsal force. This makes them difficult to manoeuvre and direct the tip. There is not an ideal handpiece available yet to control the fiber. This novel handpiece facilitates smoke evacuation at the tip improving the line of sight and smell in the OR. It has strongly improved ergonomics compared to the simple handpieces that are already available. The need for smoke evacuation is necessary as it contains over 62 toxic and biochemical components[16]. A basic study on surgical smoke found that ablating 1 g (= 1cm^3) of tissue by a CO_2 laser contains the smoke of three unfiltered cigarettes [17]and will be no different for other ablative lasers or electrosurgical equipment. As we proceed to a tobacco smoke free environment it is obvious that surgical smoke should also be reduced as much as possible. Especially in the field of open laser surgery, the development of laser fiber handpieces is far behind. Clinical evaluation in the nearby future will proof the effectiveness of this handpiece. Also in parallel, the incorporation of the hollow wave guide CO_2 laser fiber will be explored. The market potential of this handpiece will be enlarged as it facilitates a variety of laser fibers. The novel handpiece can also be introduced for the treatment of condylomata acuminata in urology and gynaecology. The effective smoke evacuation and ergonomics make it an attractive instrument as it enables perfect control of the fiber. Also, steerability of the fiber tip is improved as the distal end of the handpiece end is slightly bend. In the future, the handpiece will also be suitable for CO_2 laser hollow wave guide fibers.

FUTURE PERSPECTIVES

From the infra-red lasers that have been discussed in this thesis, the Thulium laser is the latest and most innovative one due to its high energy absorption in water, and low OH fiber delivery. Until now, no other laser has such a high absorption in water and has the ability to deliver the laser light through low OH fibers. This creates good potential for endoscopic surgery. The Thulium laser has the highest energy absorption in water for all fiber delivered lasers and is therefore a good choice for ablative endoscopic laser surgery through user friendly low OH fibers with CO_2 like properties. The Thulium laser enables ablative surgery in hard-to-reach areas such as in the brain and even in the small milk ducts. Laser fibers are ideal for endoscopic applications due to the small dimensions which enables easy access through the working channel of an endoscope. In many cases the Thulium laser can replace electrosurgery. One major advantage of laser versus electrosurgery in endoscopy, is the absence electrical currents. This prevents the risk of unwanted burns to the patient caused by leakage current or alternative electrical pathways along damaged endoscopic instruments. Other endoscopic applications such as hysteroscopic procedures would be suitable for Thulium laser usage. Especially in the treatment of intra-uterine synechiae (intrauterine adhesions, Asherman's syndrome), the Thulium laser would be an excellent device for tissue ablation. The Nd:YAG laser has been proposed for intrauterine usage but was rejected due to the deep light penetration and risk of perforation as urologists did[18].

Lasers are still relatively unknown for hysteroscopic use. The Thulium laser is a precise and haemostatic instrument and can be a good alternative for monopolar surgery in hysteroscopy. For monopolar surgery, glycine and sorbitol solutions for nonelectrolyte medium are necessary. These solutions however are hypotonic and can cause hypo osmolality and hyponatremia which in extreme cases can be fatal (slightly comparable to the TUR syndrome). Future clinical studies have to be performed to demonstrate the potential of the Thulium laser in hysteroscopic procedures.

Laser fibers can be produced very thin and still deliver sufficient power (5-10W) to be useful in very small working channels as from the ductoscope (<0.45mm). Clinical studies are needed to demonstrate if improved laser intervention in the milk ducts can diminish the recurrence of intra ductal papillomas. Also, the ablations of pre-malignant lesions can be explored.

For intra oral surgery the Thulium laser has advantage over electrosurgery especially for tumor surgery of the tongue. The absence of muscle contraction by the use of laser compared to electrosurgery has several potential benefits such as a better overview of the operating field and less bleeding due to minimal tissue manipulation. In the best case, the consequence of better surgical control is the possibility of avoiding invasive lip splitting and mandibulotomy. Also, the Thulium laser is highly suitable for tonsillectomies. The small vasculature can be easily cut and coagulated by the Thulium laser. The novel handpiece can also contribute to optimal Thulium laser usage in oral surgery as surgical smoke is removed more effectively and ergonomics are improved.

With the development of thulium lasers where fibers are used as medium to generate the laser light ('fiber laser'), new lasers systems will be more compact with higher (peak) powers. This will make them more versatile with the potential to replace other laser system like the CO_2 and Ho:YAG laser.

To conclude, there are more clinical applications in which the Thulium laser could be used for than the common current practice. The clinical field still has to discover more benefits from this laser wavelength. There is a bright future for the Thulium laser for various applications when more surgeons become aware and appreciate the special characteristics/features e.g. control of bleeding, extend of coagulation zone and the fiber delivery of this laser.

8

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9

SUMMARY
SAMENVATTING

SUMMARY

Thermal energy is commonly used for surgery to control bleeding of the surgical plane. Many sophisticated techniques are used for preventing and stopping blood loss during surgery. Electrosurgery is one of the most used and one of the most common instruments in the operating theatre. It can be applied via many different sorts of instruments for many applications. Electrical currents are generated in a high frequency, which does not interfere with nerve stimulation. Besides electrosurgery, also other devices are used to create thermal effects based on various other physical principles, such as Radio Frequent Ablation (RFA), Ultrasonic, High-intensity Focussed Ultrasound (HIFU), plasma coagulation, microwave, high pressure waterjet and electroporation.
Also, laser is used as an energy device for surgical applications. Lasers are unique light sources by emitting a small parallel beam of intense monochromatic light. This enables a high intensity at a small surface area inducing high temperature by absorption of light at the surface.
Surgical lasers in the near and mid infrared spectrum (1470nm and above) are of interest for soft tissue excisions due to the high energy absorption in water, thus preventing heat conduction into the depth of the tissue. However, these lasers have strong differences in laser tissue effect and should be carefully considered before using in clinical practice. Since 2005, the Thulium laser has been clinically introduced. It has the highest wavelength (2013nm) that can be delivered through optical fibers. The aim of this thesis is to evaluate the advantages and additional value of the Thulium laser compared to other existing energy devices.

In **chapter 2** an overview is provided of the medical applications of the Thulium laser. A systematic bibliographic search was performed in Medline. 216 studies were retrieved in 8 clinical specialties and 20 interventions/applications. The Thulium laser was used in the following specialties: urology, ear/nose/throat surgery, dermatology, neurosurgery, gastro intestinal, lungs, gynaecology and ductoscopy (breast). Most experience has been gained in urology, followed by ear/nose/throat, dermatology and neurosurgery for cutting and coagulation in open and endoscopic procedures. There is a high potential for the Thulium laser in endoscopic procedures as the laser light is fiber delivered and thus endoscopic working channels are very accessible for this type of energy delivery device. For open surgery applications, dedicated surgical tools need to be developed. Many studies described successful feasibility studies, but studies that discussed the limitation regarding coagulation and hemostatis were minimal. No basic studies have been found, describing safety margins of blood vessel coagulation without clamping.

In **chapter 3, 5 and 6,** the color Schlieren method was used for visualizing the extent of temperature gradients in tissue models in a qualitative way. In the Schlieren setup it is possible to visualize thermal gradients in an aqueous environment. This method does not measure absolute temperatures but it perfectly shows the discrete region of a temperature gradient between room temperature and 100°C.

Endoscopic third ventriculostomy is used to treat hydrocephalus. The floor of the third ventricle is fenestrated either mechanically, with electrosurgery or with laser. All techniques for endoscopic third ventriculostomy harbour the risk of damaging deeper structures such as the basilar artery that is in close vicinity of the floor of the third ventricle. Different laser wavelengths have been proposed over the last decade.
Chapter 3 evaluates the heat penetration of Thulium laser irradiation for laser-assisted endoscopic third ventriculostomy in an *in vitro* color Schlieren setup. The *in vitro setup* mimics the third ventricle environment, with a sheet gelatin as third ventricle floor and Ringer's lactate solution as aqueous medium. The Thulium laser was set at four different power settings: 1W, 2W, 4W and 7W. Beneath 4W the heat penetration was very low. To demonstrate the safety of the Thulium laser in endoscopic third ventriculostomy, a retrospective clinical study was performed on the clinical outcome of 106 patients. All of the patients had a successful fenestration, observed per operatively without complications during surgery. 1 patient had a repeated Thulium laser endoscopic third ventriculostomy within 4 months. From the 90 patients remaining in the study, 19% received a VP Shunt. The complication rate was 5% post operatively. Thulium laser assisted endoscopic third ventriculostomy can be considered safe in the 1.0-3.5W range due to shallow heat penetration.

Chapter 4 describes an *ex vivo* feasibility study of endoscopic intraductal Thulium laser ablation of the breast. Ductoscopy is a minimally invasive endoscopic approach of the milk ducts of the breast via the nipple. Besides diagnosis in women with pathologic nipple discharge, it allows non-invasive removal of intraductal lesions with a stalk like papilloma. Removal, however, is often incomplete and flat lesions cannot be targeted. We therefore developed laser ductoscopy.
Thulium laser ductoscopy was assessed on thirteen mastectomy specimens with power settings of 1-5W with 100-1000ms pulses guided through a 375µm outer diameter low OH laser fiber. Endoscopic view could be maintained during laser ablation with 1-3W.

At 3W, shrinkage of a small ductal branch could be achieved. Increasing power up to 5W causes impaired vision due to shrinkage of the main duct around the ductoscope tip. Subsequently, histology was obtained from the Thulium laser irradiated breast tissue. Median thermal damage was 1.0mm, ranging from 1.0 to 2.0mm. Based on the properties of endoscopic-control and low penetration depth, transductal thulium laser ablation was deemed safe for *in vivo* use at settings of 1-5W.

Chapter 5 and 6 describe the use of two infrared lasers for stapedotomy. Stapedotomy is a procedure to improve hearing in patients with otosclerosis. As a part of the procedure a fenestration is made in the footplate of the stapes. This is traditionally done with a drill system. Alternatively, laser systems are used for fenestrating the stapes foot plate. The diode 1470nm laser and the diode 980nm laser have been investigated in an inner ear model for the use of stapedotomy. The mechanical, thermal and acoustic effects can be observed. The inner ear model consists of a slab of polyacrylamide gel positioned between 2 glass windows. A 3 mm deep artificial vestibule is created in the gel and filled with NaCl 0.9%, mimicking the perilymph. A fresh frozen human cadaver stapes is placed on top. This inner ear model is positioned in a color Schlieren setup for imaging thermal effects. A hydrophone is placed 1cm below the stapes footplate for measuring sound production of the individual lasers pulses.
In this study pulse settings of 3W 100ms were used, for both lasers. The 980nm diode laser wavelength is strongly absorbed in pigmented areas. The white footplate of the stapes is not pigmented. Therefore, the fiber tip is carbonized prior to irradiating the stapes. Only minimal mechanical effects (small flow of NaCl) are seen in the vestibule. The 1470nm diode laser pulse produces small vapor bubbles that are pushed into the vestibule, creating an evident flow of NaCL in the vestibule. These small vapor bubbles congregate into one central bubble that is pushed further into the vestibule.
The thermal effect of the 980nm diode laser in the Schlieren setup was minimal during the fenestration. When the laser was irradiated through an existing fenestration little heat penetration was seen into the vestibule. The thermal effect of the 1470nm diode laser was small during fenestration. However, a second laser pulse created a downward flow due to the movement of the vapor bubbles, which created an evident heating pattern into the deep of the vestibule.
The acoustic effect of the 980nm laser had an average of 52±7.8 dB(A). The sound production of the 1470nm diode laser was 93±8 dB(A).
The diode 980nm laser is a useful tool in performing laser-assisted stapedotomy. Mechanical, thermal and acoustic effects are minimal. The 1470nm diode laser has large mechanical, thermal and acoustic effects in the inner ear. These effects are

caused due to the bubble formation in the vestibule. We strongly discourage to use the 1470nm diode laser for stapedotomy due to an increased risk of damaging the inner ear structures.

Chapter 7 describes a novel handpiece for open laser surgery with integrated smoke evacuation. The use of open laser surgery is upcoming but until now the choice in laser fiber handpieces is very limited. During open laser surgery, surgical smoke is produced, containing toxic components and blocking the surgeons view. Standard commercially available handpieces are often resterilizable instruments with replaceable tips and other small parts that are difficult to clean and sterilize. Also, these parts can get lost during the cleaning process. Standard handpieces do not facilitate efficient surgical smoke evacuation. There is a need for a more ergonomic laser fiber handpiece that is also capable of evacuating the surgical smoke. Designing the product as a single use product solves the problems that are associated with a resterilizable handpiece. The handpiece is designed after interviewing head and neck surgeons who frequently use the Thulium laser for intra oral resections. A prototype has been made and tested in an in vitro setup. A 3D printed prototype laser fiber handpiece was tested for smoke evacuation effectiveness by lasing on a homogenous piece of meat. Stroboscope light enhanced the visibility of the smoke, and video recordings were evaluated for visual presence or absence of laser smoke. The handpiece was able to evacuate all the produced smoke visually. Future design iterations will incorporate the possibility for the use of hollow wave guide CO_2 fibers. A clinical device will be developed with subsequent testing.

General discussion

Chapter 8 contains the general discussion and future perspectives of clinical lasers in the infrared region. The infrared region is very interesting as it is a wide region (810nm-10.600nm) with many kinds of laser tissue interaction. The Thulium laser (2013nm) is a relatively new laser in this region and could safely replace the 810 and 1064nm lasers for laser assisted third ventriculostomy. It is no longer necessary to pre-carbonize the laser fibers of the 810nm and 1064nm laser as the Thulium laser has direct absorption of the light in soft tissue (water) with a reproducible effect. It has good potential for endoscopic surgery in general as the laser has the ability to deliver the laser light through low OH fibers with CO_2 laser like properties. It fits through nearly every working channel due to the small dimensions of the laser fiber. For intra oral surgery the Thulium laser has an advantage over electrosurgery, especially for tumor surgery of the tongue. The absence of muscle contractions by the use of laser compared to electrosurgery

has several potential benefits such as better overview of the operating field and less bleeding due to minimal tissue manipulation. In de best case, the consequence of a better surgical control is the possibility of avoiding invasive lip splitting. Also the Thulium laser is very suitable for tonsillectomies. The small vasculature can be easily cut and coagulated by the Thulium laser. The novel handpiece with integrated smoke evacuation can also contribute to optimal Thulium laser usage in oral surgery.
The development of the Thulium 'fiber' lasers might make new laser systems available with higher powers. This might have the potential to replace other laser systems like the CO_2 laser and the Ho:YAG laser.
The clinical field still has to discover more benefits from the Thulium laser as there are more clinical applications in which the Thulium laser could be used for. There is a bright future for the Thulium laser for various applications when more surgeons become beware and appreciate the special characteristics and features of this laser.

9

SAMENVATTING

Thermische energie wordt tijdens chirurgie vaak gebruikt om hemostase (bloedstelping) te verkrijgen. Veel verfijnde thermische technieken zijn beschikbaar om bloedverlies te voorkomen, maar ook om tumoren te behandelen. Electrochirurgie is één van de meest gebruikte en meest voorkomende apparatuur van de operatiekamer en kan met behulp van diverse instrumenten voor veel verschillende klinische toepassingen worden gebruikt. Bij electrochirurgie worden elektrische stromen met een hoge frequentie gegenereerd, waardoor er geen interferentie ontstaat in de zenuwgeleiding. Naast electrochirurgie bestaat er ook andere apparatuur voor het opwarmen van weefsel ten behoeve van coagulatie en/of ablatie. Deze apparatuur is gebaseerd op verschillende fysische principes zoals Radio Frequente Ablatie (RFA), Ultrasoon mes, High-Intensity Focussed Ultrasound (Hoog intensiteit gefocusseerd ultrageluid), microgolf, plasma coagulatie, hoge druk water straal en electroporatie.
Laser wordt ook als energie bron gebruikt voor chirurgische toepassingen. Lasers zijn unieke lichtbronnen die een smalle intense parallelle bundel van monochromatisch licht produceren. Dit kan een klein oppervlak zeer sterk verhitten. Door absorptie van het licht in het weefsel.
Chirurgische lasers in het nabij- en middel-infrarood spectrum zijn interessant voor zachte weefsel resecties. Bij klinische lasers met een golflengte vanaf 1470nm en hoger is er een hoge absorptie van energie in water (zachte weefsels bevatten meer dat 60% water) waardoor de energie niet ver het weefsel indringt en aan het oppervlak blijft. Er zijn echter wel sterke verschillen in weefsel effect bij de verschillende lasers in infrarode gebied. Daarom moet goed onderzocht worden welke laser veilig voor een specifieke toepassing gebruikt kan worden. In 2005 is de Thulium laser (2013nm) klinisch geïntroduceerd. Het licht van deze golflengte kan door optische fibers geleid worden. Boven deze golflengte wordt het licht geabsorbeerd in glas en zal het laser licht via een gearticuleerde spiegel arm geleid moeten worden, zoals bij de CO_2 laser.
Het doel van dit proefschrift is om de toegevoegde waarde van de Thulium laser te onderzoeken ten opzichte van andere energie bronnen ten behoeve van coagulatie en/of ablatie.

In **hoofdstuk 2** wordt een overzicht gegeven van de huidige medische toepassingen van de Thulium laser. Er zijn 216 studies gevonden bij 8 verschillende specialismen en 20 verschillende toepassingen. Bij de volgende specialismen werd de Thulium laser gebruikt: urologie, keel/neus/oorchirurgie, dermatologie, neurochirurgie, gastro intestinale toepassingen, longchirurgie, gynaecologie en ductoscopie in de melkgangen van de borst. De meeste ervaringen is opgedaan in de urologie, gevolgd door de keel/neus/oorchirurgie, dermatologie en de neurochirurgie voor zowel open als endoscopische chirurgie. De Thulium laser is zeer geschikt voor endoscopische chirurgie vanwege de dunne laser fibers die door bijna elk werkkanaal van endoscopen passen. Voor open laser chirurgie is het instrumentarium onvoldoende ontwikkeld en moet er een speciaal handstuk worden ontwikkeld. Er zijn veel succesvolle haalbaarheidsstudies uitgevoerd, maar er is weinig fundamenteel onderzoek gedaan naar de beperkingen van het gebruik van de Thulium laser op het gebied van coagulatie/hemostase.

In **hoofdstuk 3,5 en 6** wordt de kleuren Schlieren methode gebruikt om temperatuur gradiënten te meten in weefselmodellen/*in vitro* opstellingen. Het is hierbij mogelijk om temperatuurgradiënten te visualiseren in een water omgeving. Deze methode kan geen absolute temperaturen meten maar het kan wel zeer goed te verschillen in temperatuur verloop laten zien tussen kamertemperatuur en 100°C.
In **hoofdstuk 3** wordt de warmte verspreiding van de Thulium laser beschreven d.m.v. een *in vitro* color Schlieren methode bij een endoscopische derde ventriculocisternostomie. Bij deze ingreep wordt hydrocefalus behandeld. Er wordt hierbij met behulp van een laser een fenestratie gemaakt in de bodem van het derde ventrikel. Bij alle technieken (mechanisch, electrochirurgie en laser) die klinisch gebruikt worden bij deze methode, is er gevaar op beschadigingen aan omliggende kwetsbare structuren. Met name de arteria basilaris is kwetsbaar, omdat deze zeer dicht langs de bodem van het derde ventrikel is gelegen. In de laatste decennia zijn hiervoor verschillende lasersystemen (golflengtes) voor gebruikt. De *in vitro* opstelling die gebruikt is om de Thulium laser te onderzoeken, is een model voor het derde ventrikel. Een gelatine blaadje bootst de bodem van het derde ventrikel na. Als vloeistof wordt Ringer Lactaat oplossing gebruikt. De diepte van de warmte penetratie onder het weefselmodel van de Thulium laser wordt gemeten en daarbij worden vier verschillende vermogens instellingen gebruikt: 1W, 2W, 4W en 7W. Onder de 4W is de warmte penetratie zeer laag. Voor het aantonen van de klinische veiligheid van de Thulium laser bij derde ventriculocisternostomieën is er een retrospectieve klinische studie uitgevoerd bij 106 patiënten. Bij alle patiënten was er een succesvolle fenestratie uitgevoerd door middel van peroperatieve bevindingen. Bij 1 patiënt moest er binnen 4 maanden na de eerste Thulium laser fenestratie opnieuw een fenestratie worden uitgevoerd. Van de 90 patiënten die overbleven in de studie kreeg 19% een ventrikel peritoneale shunt. De post operatieve complicatie score was 5%. Geconcludeerd kan worden dat er tussen de 1,0 en de 3,5W op een veilige manier een derde ventriculocisternostomie gemaakt kan worden.

Hoofdstuk 4 beschrijft een *ex vivo* haalbaarheid studie van endoscopische intraductale Thulium laser ablatie van de borst. Ductoscopie is een minimaal invasieve endoscopische benadering van de melkgangen van de borst via de tepel. Op deze manier kan er diagnostiek worden uitgevoerd bij pathologische tepeluitvloed. Ook intraductale papillomen kunnen worden verwijderd. Helaas kunnen poliepen niet altijd in hun geheel worden verwijderd en vlakke laesies kunnen met de huidige methodes niet worden verwijderd. Laser ductoscopie is ontwikkeld om moeilijk te verwijderen poliepen te vaporiseren en vlakke laesies te verwijderen.
Thulium laser ductoscopie is uitgevoerd op dertien mastectomie preparaten waarbij 1 tot 5W met laser pulsen van 100 tot 1000ms zijn gebruikt. Hierbij is een lage concentratie OH fiber gebruikt met een buiten diameter van 375µm. Tot vermogens van 3W is endoscopisch zicht goed mogelijk en is het mogelijk om de kleinere melkgangen dicht te coaguleren. Tussen 3 en 5W wordt het zicht belemmerd doordat de hoofdduct door coagulatie dicht krimpt. Histologie is uitgevoerd op het weefsel dat met de Thulium laser is behandeld. De gemiddelde thermische schade was 1.0mm met een maximum van 2.0mm diepte. Op grond van de resultaten waarbij is gekeken naar het zicht tijdens de ingreep, warmte penetratie diepte, is bepaald dat laser parameters van 1 tot 5W veilig gebruikt kunnen worden bij *in vivo* gebruik.

Hoofdstuk 5 en 6 beschrijven het gebruik van twee verschillende infrarood lasers voor stapedotomie procedures. Een stapedotomie wordt uitgevoerd bij patiënten met otosclerose om de gehoorfunctie te verbeteren. Een deel van deze ingreep bestaat uit het maken van een fenestratie in de voetplaat van de stapes. De meest gangbare manier om dit te doen is door middel van een heel klein boorsysteem, maar het kan ook worden uitgevoerd door een lasersysteem. De 1470nm en de 980nm laser zijn in een *in vitro* binnenoor opstelling onderzocht voor het gebruik tijdens een stapedotomie. Hierbij zijn de mechanische, de thermische en de akoestische effecten onderzocht. Het binnenoor model bestaat uit een plakje polyacrylamide gel dat geklemd is tussen twee glaasjes. Het kunstmatige vestibulum van 3mm diep is uitgesneden uit de gel en opgevuld met een fysiologische zout oplossing. Daarboven is een humane ingevroren stapes geplaatst. Het binnenoor model is in de Schlieren opstelling geplaatst voor het meten van de thermische effecten en 1 cm onder de stapes voetplaat is een hydrofoon geplaatst om de geluidsproductie te meten van de individuele laser pulsen.
Bij deze studies zijn voor beide lasers, pulsen gebruikt van 3W met een puls lengte van 100ms. Licht met een golflengte van 980nm wordt goed geabsorbeerd in gepigmenteerde weefsels maar niet in licht gekleurde weefsels zoals bot. Om deze rede is de fiber tip zwart gemaakt d.m.v carbonisatie, waardoor er warmte wordt afgegeven

aan de stapes voetplaat. Er zijn minimale mechanische effecten waargenomen (een hele lichte stroming fysiologische zout oplossing) in het vestibulium model. Bij de 1470nm laser ontstaan kleine dampbellen die in het model van het vestibulum worden gedrukt waardoor er een duidelijke flow van de vloeistof ontstaat. Deze kleine dampbellen voegen zich samen in één dampbel die nog verder in het vestibulum model beweegt.
Het thermische effect tijdens de fenestratie van de 980nm diode laser is minimaal in de Schlieren opstelling. Op het moment dat er door de fenestratie een laser puls wordt afgegeven, is er een minimale warmteontwikkeling zichtbaar in het vestibulum. Bij de 1470nm diode laser is het warmte effect bij de eerste puls laag, maar een tweede laser puls veroorzaakt een stroming in het vestibulum door dampbelvorming met bijbehorende warmte ontwikkeling.
Het geluidsniveau van de 980nm diode laser bedroeg gemiddeld 52±7.8 dB(A). Het geluidsniveau van de 1470nm bedroeg gemiddeld 93±8 dB(A).
De 980nm diode laser is een goed instrument voor laser stapedotomieën. De mechanische, thermische en de akoestische effecten zijn minimaal. De 1470nm diode laser heeft grote mechanische, thermische en akoestische effecten doordat er dampbellen ontstaan in het vestibulum model. De 1470nm diode laser wordt afgeraden voor laser stapedotomieën.

In **Hoofdstuk 7** wordt een nieuw handstuk voor open laser chirurgie met geïntegreerde rookafzuiging beschreven. Open laser chirurgie wordt steeds meer gebruikt, maar net zoals bij electrochirurgie komt er chirurgische rook (met veel schadelijke componenten) bij vrij. De keuze in handstukken die de laser fiber geleiden is beperkt. De verkrijgbare handstukken bestaan uit meerdere kleine hulpstukken die moeilijk te reinigen en te steriliseren zijn. Deze kleine onderdelen kunnen tijdens het reinigingen gemakkelijk verloren gaan. De standaard beschikbare handstukken beschikken daarbij ook niet over rookafzuiging. Met de toenemende behoefte aan open laser chirurgie komt er steeds meer vraag naar een handstuk met geïntegreerde rookafzuiging. Bij het ontwerp van een nieuwe laser fiber handstuk is er een programma van eisen opgesteld naar aanleiding van interviews met gebruikers van de Thulium laser voor de resectie van intra orale tumoren. Er is een 3D prototype gemaakt van een laserfiber handstuk met geïntegreerde rookafzuiging. De effectiviteit is onderzocht in een *in vitro* opstelling, waarbij de Thulium laser is toegepast op een stuk homogeen vlees. Door middel van een stroboscopische belichting is het mogelijk de chirurgische rook te visualiseren en vast te leggen met behulp van video opnames. De video opnames zijn beoordeeld op de aan en afwezigheid van de chirurgische rook. De video opnames lieten zien dat het handstuk alle geproduceerde rook kon verwijderen. Er wordt een klinisch laser fiber handstuk gemaakt dat klinisch getest zal gaan worden. In de toekomst zal het ontwerp geschikt gemaakt worden voor hollow wave fibers ten behoeve van de CO_2 laser.

Algemene discussie

Hoofdstuk 8 bevat de algemene discussie en de toekomst perspectieven van de klinische lasers in het infrarode gebied. Het infrarode gebied is een interessant gebied vanwege de verscheidenheid aan systemen en de verschillen in laser-weefsel interactie. De Thulium laser (2013nm) is een relatief nieuw systeem in het infrarode gebied en kan de 810 en de 1064nm lasers op een veilige manier vervangen voor aantal specifieke toepassingen. Het is daarbij dan niet meer nodig om de laser fiber voor het gebruik te voorzien van een carbonisatie laagje. De Thulium laser heeft een directie absorptie van energie in water en zachte weefsels met een reproduceerbaar effect. De Thulium laser is zeer goed te gebruiken in endoscopische chirurgie vanwege het feit dat het Thulium laser licht door glas fibers geleid kan worden. Hierdoor is er een laser beschikbaar gekomen met CO_2 laser eigenschappen. Het grote voordeel van fiber geleid laserlicht is dat de dunne laser fibers door bijna elk werkkanaal van de endoscoop passen en daardoor voor veel klinische toepassingen gebruikt kan worden. Voor intra orale chirurgie heeft de Thulium laser als grote voordeel dat bij het excideren van tongtumoren de spiercontractie afwezig is tegenstelling bij het gebruik van electrochirurgie. Hierdoor ontstaat een beter overzicht van het operatiegebied en er zijn minder bloedingen door minimale weefselmanipulatie. In het beste geval kan door deze techniek de lip split procedure worden voorkomen tijdens een mondbodem tumor resectie. De Thulium laser is ook geschikt voor het tonsillectomieën. De kleine vasculatuur kan goed door de Thulium laser worden doorsneden en gecoaguleerd. Het nieuw ontwikkelde handstuk met geïntegreerde rookafzuiging zal bijdragen aan het optimaal gebruik van de Thulium laser bij intra orale chirurgie.
De ontwikkeling van de Thulium ‘fiber’ lasers zou het mogelijk kunnen maken om laser systemen te maken met hogere vermogens waardoor andere lasers zoals de CO_2 en de Ho:YAG vervangen zouden kunnen worden.
Binnen de chirurgie zijn er nog veel nieuwe toepassingen waarbij de Thulium laser gebruikt kan worden. De toekomstverwachting van deze laser is zeer goed als de snijdende specialisten meer de voordelen gaan inzien van de toepassingsgebieden van de Thulium laser.

9

ADDENDUM

COMPARING THULIUM LASER AND ND:YAG LASER

In the Treatment of Genital and Urethral Condylomata Acuminata in Male Patients

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ABSTRACT

Background
To date therapies for condylomata acuminata of the male genital are known for high recurrence rates and bothersome side-effects, while urethral warts are not always reachable by most traditional therapies.

Objective
To compare the clinical outcomes in the treatment of condylomata acuminata on the male external genitalia and/or urethra using the Thulium laser and the Neodymium:Yttrium Aluminum Garnet laser.

Methods
From January 1994 to January 2013, 76 men with condylomata acuminata on the external genitalia or within the urethra were treated with the Nd:YAG laser and 39 men with the Thulium laser. Primary clearance rate, relapse characteristics and complications were investigated retrospectively and compared.

Results
Of the total of 115 patients, 39 patients (34%) developed recurrences, of which 13 in the Thulium laser group en 26 in the Nd:YAG laser group. Two patients in the Thulium group and four in the Nd:YAG group had minor complications.

Conclusion
This first report of the treatment of condylomata acuminata with the Thulium laser shows that it is a safe and effective treatment for condylomata, both on the external genitalia and in the urethra. The recurrence rate is comparable to the Nd:YAG laser and there have been minimal complications as a result of minimal scarring.

Key words
condylomata acuminata; genital; laser; Neodymium:Yttrium Aluminum Garnet; Thulium; urethra

INTRODUCTION

Condylomata acuminata (CA) or genital warts are benign proliferative lesions caused by the human papillomavirus (HPV), typically types 6 and 11. They are the most common sexually transmitted infection treated at genitourinary medicine clinics. There is a transmission rate of almost 60% between partners during one time sexual intercourse[1,2].
Approximately 20% of all genital warts are found in the urethra, especially in the external meatus of the urethra. A positive urethral sampling for HPV is found in about 10% of the male population between 18 and 40 years old[3,4].

The choice of treatment depends on the number, size, site and morphology of the lesions as well as patient preferences, cost, convenience, adverse effects, clinical experience and availability. Traditional therapies include podophyllotoxin, imiquimod, trichloroacetic acid, surgical excision, cryotherapy and electrosurgery. Generally, recurrence rates are high. Unfortunately, these are even higher when urethral condylomata are involved, which sometimes need endoscopic access for treatment. Moreover, excision, cryotherapy and electrosurgery often result in a considerable amount of scarring. Therefore, alternative methods are being developed, including laser therapy; however, only a few of these methods can be used during endoscopy [2,5,6].

The Neodynium:Yttrium Aluminum Garnet (Nd:YAG) and Thulium laser are both lasers that can be used for external CA and for urethral CA during endoscopy. The Nd:YAG laser has frequently been reported for the treatment of CA, in contrast to the Thulium laser, which is a relatively new surgical continuous wave laser. The Thulium laser has a wavelength of 2.0μm, allowing the wavelength to match the 1.92μm water absorption peak in tissue. The high density of absorbed energy at the tissue surface leads to instant vaporization and limits the penetration depth to 500-2000μm, depending on the power settings, which is a reasonable depth for sufficient hemostasis with minimal thermal injury to surrounding tissue. The light is generated as a continuous wave[7].

To date, there have been no reports on the use of the Thulium laser in the treatment of CA or on the comparison of this treatment with the Nd:YAG laser treatment of CA. This report describes the treatment of 115 male patients with CA that were treated with laser from January 1994 to January 2013. The Nd:YAG laser (Nd:YAG group) was used in 76 patients and the Thulium laser (Thulium group) in 39 patients. The primary clearance rate, relapse characteristics and complications were investigated and compared between the two lasers.

MATERIAL AND METHODS

Patients

A retrospective analysis was made of the records of all male patients presented with CA at our department that were treated with either the Nd:YAG or Thulium laser from January 1994 to January 2013 (n=115). Medical history was checked with a special emphasis on age, sexual relationship, lower urinary tract symptoms, hematuria, bleeding from the urethral meatus, previous treatments and concomitant diseases.

The diagnosis of CA was based on clinical presentation and biopsy with histological confirmation. Before October 2005, all patients (n=76) were treated with the Nd:YAG laser; from October 2005 the Thulium laser was used (n=39).

Equipment

After urethral instillation of lidocaine jelly (Instillagel, Farco Pharma, Germany), a Ch.22 endoscope with Albarran bridge (Figure 1) was used to perform the endoscopy and, if urethral CA were found, to guide the laser fiber for laser treatment.

The Nd:YAG laser unit (type VersaPulse PowerSuite Holmium/Nd:YAG, Coherent, USA) had a 600μm laser fiber with a variable power setting of 5-30Watts, operating in continuous-wave mode. Two types of Thulium lasers were used (The Revolix duo 70 W, with a variable power setting of 5-70Watts LISA laser, Germany. And the Revolix junior, with a variable power setting of 1-15Watts LISA laser, Germany). Both lasers were operated with a reusable 550μm silica laser fiber, operating in continuous-wave mode. Proper precautions were used when using the laser including eye protection, smoke evacuation and FFP3 smoke protection masks.

Treatment

All patients were treated under spinal or general anesthesia. During the operation the patients were in the lithotomy position. Extensive examination of the external genitalia was performed. If necessary, the meatus was dilated with a small nasal speculum; moreover, each patient underwent cystoscopy. A cold biopsy or excision of the suspect lesion was taken for histology, and subsequently the rest of the lesion and any other visible lesions were vaporized with the laser. This gives the typical white blanching of the lesion (Figure 2). Patients with spinal anesthesia or extensive urethral lesions received an indwelling catheter for one night.

Patients stayed in the hospital for a maximum of one night. All patients were invited for follow-up within three months. If any urethral lesions were found during the operation, the cystoscopy was repeated. If patients had presented with an extensive degree of CA, multiple sessions of Thulium laser treatment were planned. For the three months following the operation, condom use was advised during sexual intercourse.

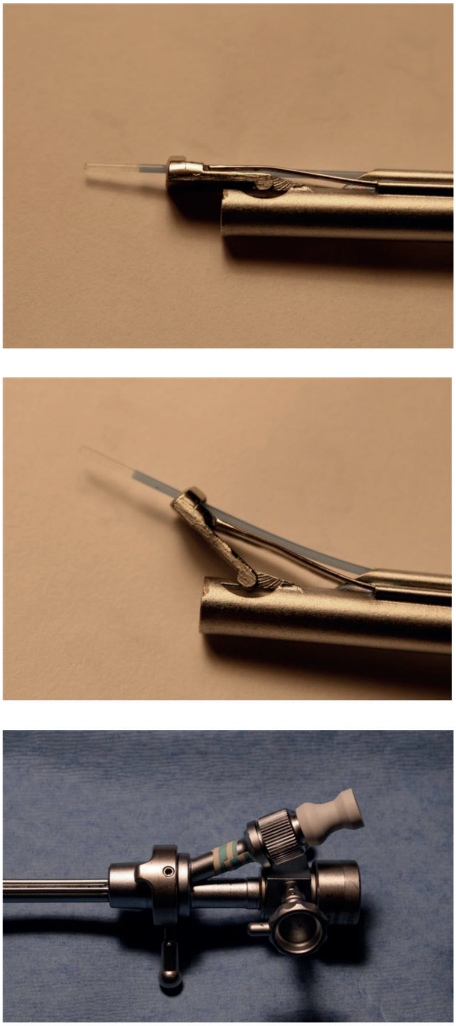

FIGURE 1. Laser Albarran (Storz). The tip of the laser fiber (photo 1A and B) can be moved under endoscopic sight by turning the tuning knob (photo 1C) making it easier to aim the tip on the lesion, with dimensions of the angel from 180 till 120°.

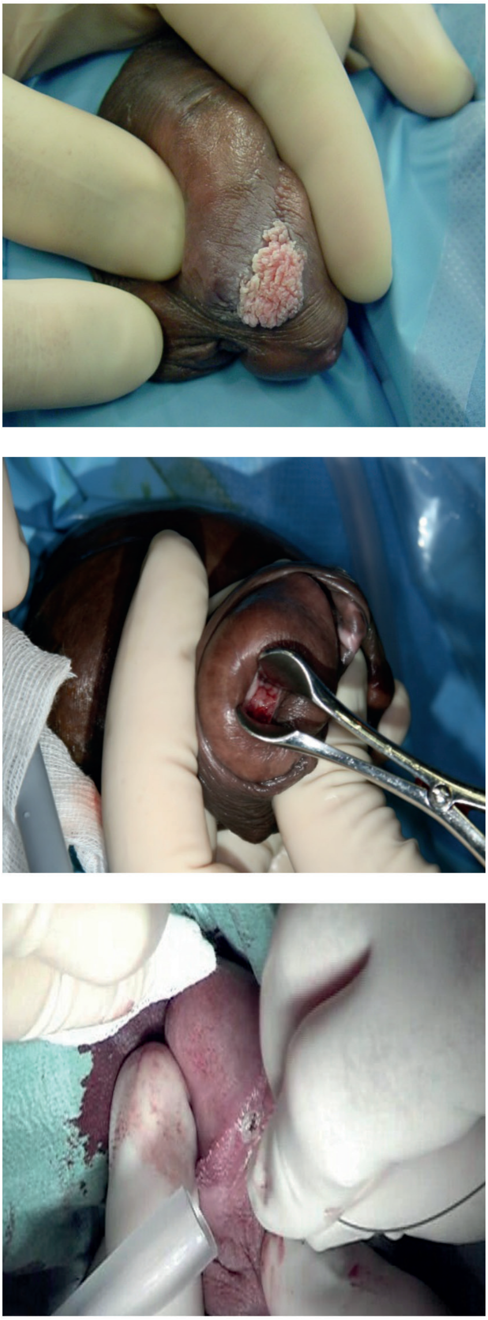

FIGURE 2. Thulium laser treatment of condylomata acuminata on the male genital. A: Condylomata acuminata on the glance of the penis. B: Inspection of the meatus with a small nasal speculum shows distal urethral condylomata acuminata. C: Coagulation of condylomata acuminata with the Thulium laser showing the white blanching of the lesion.

RESULTS

The results of all patients are listed in table 1 and 2. The patients' mean age at presentation was 30.4 years (range 19-65 years) and was comparable for the Thulium and the Nd:YAG group.

In the Nd:YAG group, three patients were HIV-positive and one had diabetes mellitus. In the Thulium group, one patient was receiving immunosuppressant therapy due to a kidney transplant, two patients were HIV-positive and were receiving HAART-therapy, one of whom also had a history of a kidney transplant, and two patients had diabetes mellitus.

In the Thulium group, there were significantly more patients with CA on the external genitalia (i.e. shaft of the penis, scrotum, foreskin, inguinal and/or suprapubic region), but the distribution between the groups of urethral CA (including meatal CA) was comparable. None of the patients had CA in the bladder or proximal urethra. In both groups, the majority had multifocal CA.

Fourteen patients (12%) with urethral condylomata had no other foci of warts; however, they had symptoms of hematuria, hematospermia or signs of mild obstruction. Before the laser therapy described in this study, 71 patients (62%) had had previous treatment: podophylotoxin, imiquimod, cryotherapy, electrocoagulation, CO_2 laser treatment and/or surgical excision. Of these 71 patients, 31 (44%) had received a combination of these treatment options. In six patients it proved impossible to ascertain whether they had received any therapy before presenting at our hospital. Six other patients had received previous treatment, but it remained unclear what this treatment was.

The mean power setting in the Thulium laser group was 8.8 Watts (3-18 Watts). The total energy used varied from 20 to 7794J (mean 1508 J). In three patients, circumcision was performed with the Thulium laser, due to extensive CA on the prepuce. These three circumcisions gave the highest values of energy used. If these values were excluded, the mean energy used would be 829 J per patient. In the Nd:YAG group, in which only one circumcision was performed, the total energy used varied from 10 to 6308 J (mean 984 J), with a mean power setting of 21Watts (5-30Watts). If the circumcision was not taken into account, the mean energy used would be 895 J per patient.

TABLE 1. Pre-Treatment Characteristics of Male Patients Who Were Treated for Genital Condylomata Acuminata by Thulium Laser and Nd:YAG Laser

	All patients (n =115)	Thulium group (n = 39)	Nd:YAG group (n = 76)	P-value[a]
Age (mean years)	30.4 (SD 9.3)	28.9 (SD 8.3)	31.2 (SD 9.8)	0.22
Immunocompromised	9 (7.8%)	5 (12.8%)	4 (5.3%)	0.27
Position of CA				
Urethral meatus	69 (60.0%)	20 (51.3%)	49 (64.5%)	0.23
Urethra	48 (41.7%)	14 (35.9%)	34 (44.7%)	0.43
External genital	55 (47.8%)	24 (61.5%)	31 (40.8%)	<0.05[b]
Number of foci of warts				0.84
1 focus	22 (19.1%)	5 (12.8%)	17 (22.4%)	
2 foci	22 (19.1%)	7 (17.9%)	15 (19.7%)	
3 foci	12 (10.4%)	5 (12.8%)	7 (9.2%)	
4 foci	10 (8.7%)	3 (7.7%)	7 (9.2%)	
5 foci	5 (4.3%)	2 (5.1%)	3 (3.9%)	
>5 foci	44 (38.3%)	17 (43.6%)	27 (35.5%)	
Previous treatment	71/111 (64.0%)	26/39 (66.7%)	45/70 (64.3%)	0.73
Podophylotoxin	12/111 (11.0%)	3/39 (7.7%)	9/70 (12.9%)	
Imiquimod	1/111 (0.9%)	1/39 (2.6%)	0/70 (0.0%)	
Cryotherapy	14/111 (12.6%)	5/39 (12.8%)	9/70 (12.9%)	
CO_2 laser treatment	2/111 (1.8%)	1/39 (2.6%)	1/70 (1.4%)	
Surgical excision	3/111 (2.7%)	1/39 (2.6%)	2/70 (2.9%)	
Electrocoagulation	2/111 (1.8%)	0/39 (0.0%)	2/70 (2.9%)	
Combination therapy	31/111 (27.9%)	14/39 (35.9%)	17/70 (24.3%)	
Unknown therapy[c]	6/111 (5.4%)	1/39 (2.6%)	5/70 (7.1%)	
Missing data[d]	6/115 (5.2%)	0/39 (0.0%)	6/76 (7.9%)	

SD, standard deviation.
[a]The ages were compared using a Student's t-test; categorical values were compared using a Fisher's exact-test,
both with $P<0.05$ considered statistically significant.
[b]Significant difference; in this case 0.048.
[c]Patients who had undergone previous therapy, but for whom the modality is unknown.
[d]It is unknown whether these patients had received previous therapy.

TABLE 2. Main Treatment Outcomes of Male Patients Treated for Genital Condylomata Acuminata by Thulium Laser and Nd:YAG Laser

	All patients (n ¼ 115)	Thulium group (n ¼ 39)	Nd:YAG group (n ¼ 76)	P-value[a]
Recurrence	39 (33.9%)	13 (33.3%)	26 (34.2%)	1.00
Complications	6/115 (5.2%)	2/39 (5.1%)	4/76 (5.3%)	1.00
Meatal stenosis	5	1	4	
Urethral stricture	1	1	0	

[a]Values were compared using a Fisher's exact-test with $P < 0.05$ considered statistically significant.

TABLE 3. Type of Laser and Reported Recurrence Rates for Treatment of Condylomata Acuminata

Type of laser	Reported recurrence rates (%)
CO_2	19–33
Argon	35
Pulsed dye	5–23
Holmium[a]	Unknown[b]
Nd:YAG[a]	0–60
Thulium (this study)[a]	33

[a]Has been used for urethral condylomata acuminata.
[b]Recurrence rate has not been described, percentage of patients cured after 1 treatment varied from 16% to 55%, depending on location of the CA.

All patients went home the same day or stayed at our hospital for a maximum of one night.
A number of patients, both in the Thulium group (n=4) and in the Nd:YAG group (n=8), underwent a scheduled second laser treatment because of extensive or circular urethral CA. Of these twelve patients, four were HIV-positive; these patients needed 4, 10, 14 and 17 treatments to clear all visible CA. The other patients with pre-scheduled repeated treatment, two in the Thulium group and six in the Nd:YAG group, needed a total of 5 and 34 treatments, respectively. Thus for primary macroscopic clearance of CA in all 115 patients, 54 laser treatments were needed in the Thulium group and 102 in the Nd:YAG group.

In the Thulium group, 13 patients (33%) had recurrences that required additional laser treatment. A comparable number of patients was found in the Nd:YAG group. In the Thulium group, one patient developed meatal stenosis and one had a distal urethral stricture seen by endoscopy during follow-up; however, neither condition was urodynamically relevant. The meatal stenosis was treated by meatotomy, using the Thulium laser. The stricture of the distal urethra was treated by only dilatation. In the Nd:YAG group, four meatal stenoses were found; three needed a meatotomy and the fourth did not require treatment.

DISCUSSION

Despite the high prevalence of genital HPV infection, traditional treatment options are associated with high recurrence rates. Home therapy treatments consist of Podophyllotoxin (0.5% solution or 0.15% cream), Imiquimod (5% cream) and Sinecatechins (10-15% ointment; currently available in a growing number of countries including the United States). These treatments have reported clearance rates of 43-83%, 35-68% and 47-59%, respectively. In patients with clearing, recurrence rates have been reported of 6-100%, 6-26% and 7-11%, respectively. All these therapies require compliance in order to be effective and may have bothersome side effects.

Out patient clinic therapies are cryotherapy, with clearance rates of 44-75% and recurrence rates of 21-42%, and trichloracetic acid 80-90% solution (TCA), with clearance rates of 56-81% and recurrence rates of 36%. Only surgical therapies have primary clearance rates approaching 100%; these include electrosurgery, excision and laser therapy. Electrosurgery and excision have reported recurrence rates of 22% and 19-29%, respectively. However, these treatments may involve a great deal of scarring [2,8]. The estimated cost-effectiveness of the treatment of external genital warts is better for the surgical treatments, including laser[9]. The highest costs are incurred when a switch of therapy has been made due to failure of the initial therapy [10].

Laser therapy has been used for the treatment of CA since the 1970s. The CO_2, Pulsed dye, Argon, Holmium and Nd:YAG lasers have been described as treatment options for CA. Of these, only the Nd:YAG laser has frequently been reported as a widely-used treatment option for CA in the urethra, which can only be reached by endoscopy. In 42% of our patients urethral CA were found; therefore, it is important that endoscopy is carried out and that a good treatment option is available for these urethral CA, which, different from external CA, give more bothersome symptoms such as obstruction.

There is a large variation in reported recurrence rates in the treatment of CA, both when the same type of laser was used and when different types of lasers were used (Table 3). For the CO_2 laser, recurrence rates of 19-33% have been reported. The recurrence rates reported for the Pulsed dye laser are 5-23%, and for the Argon laser these are 35%. Only 16% of the patients with urethral CA were cured after one treatment with the Holmium laser; no clear recurrence rate has been reported for this laser. The Nd:YAG laser is the laser treatment option for urethral CA that has been described most often; for this laser, recurrence rates of 0-60% have been found[5,11-22].

To the best of our knowledge, this study is the first report of the Thulium laser used in the treatment of CA. With a wavelength of 2.0μm, this laser matches the water absorption peak wavelength in tissue, which is 1.92μm. This is the reason why the energy is absorbed at the tissue surface, resulting in instant vaporization and a limited penetration depth of 500-2000μm, and, as a consequence, in good hemostasis and minimal thermal injury[7]. The tissue effect of the continuous wave Thulium laser is comparable with the continuous wave CO_2 laser. However, the advantage over the CO_2 laser is that the Thulium laser energy can be delivered through a small silica fiber and thus can be applied effectively during endoscopic procedures. Compared to the Nd:YAG laser, the penetration depth of the Thulium laser is less, which gives the surgeon more control.

Although this study is not a randomized controlled study, we are convinced that the Thulium group and the Nd:YAG group can be compared well. Patient age and number of warts did not differ significantly, and all patients were treated under the same conditions in the same institution.

Even though it was assumed that the properties of the Thulium laser would result in fewer complications due to tissue damage, no difference was found in complication rate: in both groups the complication rates were low and no severe complications occurred.

Nor was any significant difference found in the recurrence rates of the Thulium and Nd:YAG groups. The recurrence rates found were comparable to those reported in literature for other lasers (Table 3), even though 64% of our patients had had prior therapy-resistant treatments and a substantial percentage of our group (42%) had urethral CA, which are known for their high recurrence rates[5,6].

Zaak et al. report a complication rate for the Nd:YAG laser of 9.6% due to scarring, mostly urethral stenosis, of which 64% was urodynamically relevant. Other rare complications reported were postoperative sclerosis and scars of the adjacent corpora cavernosa, even resulting in a permanent deviation of the penis[11]. More severe complications of the Nd:YAG laser treatment in genital CA have also been described; these were due to the deeper penetration resulting in deep coagulation necrosis[23].

Yang et al report on a large cohort study in which patients with genital CA were treated using the Holmium laser[5]. A disadvantage of the Holmium laser is that it is a pulsed laser instead of a continuous wave. During the 300μs pulse of the laser, water is instantly turned into an exploding vapor bubble that expands and ruptures the surrounding tissue up to several mm. This characteristic has led to the frequent use of the Holmium laser for lithotripsy. A higher amount of tissue damage is expected due to this rupture, although Yang et al did not find any complications due to scarring. This study does not report whether endoscopy was performed in the 69 patients with urethral CA. It is surprising that in this study by Yang et al, only 15.9% of the patients with urethral CA were cured after one treatment.

Our results suggest that both the Thulium laser and the Nd:YAG laser are good alternatives for the treatment of CA, on the external genitalia as well as in the urethra, especially if other treatments have failed. In our opinion, the Thulium laser is preferable because it is easier to control because of the limited penetration of energy in tissue.

In conclusion, this study shows that the Thulium laser is a safe and effective treatment option for the treatment of CA, both on the external genitalia and in the urethra, but that it is neither superior nor inferior to the Nd:YAG laser. Because of its continuous wave and characteristic wavelength, the Thulium laser is an ideal energy source for controllable vaporization and coagulation with a minor scarring rate. Therefore, in our opinion the Thulium laser is the laser of first choice.

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DANKWOORD
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LIST OF PUBLICATIONS
LIST OF ABBREVIATIONS

DANKWOORD

Bij mijn aanstelling in het UMCU ben ik min of meer in het onderwerp van dit proefschrift gerold. De Thulium laser werd dat moment geïntroduceerd en de meerwaarde werd onderzocht. In de jaren die volgden kwam ik er steeds meer achter in wat voor een geweldige omgeving ik me bevond. Enthousiaste clinici en technici met goede ideeën, maar gelukkig ook kritisch tegenwicht. Op congressen kon ik de ideeën presenteren en ik kon deelnemen aan de UREKA Mega Challenge met het onderwerp laser ductoscopie. De onvermijdelijke vraag kwam steeds weer in mij op… Ga ik het aan om een proefschrift te schrijven? Om mij heen had ik het gezien, het wordt niet makkelijk. Maar het is naar mijn idee dé manier om een nieuwe techniek in perspectief te plaatsen. Ik wil graag de mensen bedanken met wie ik heb samengewerkt en die veel voor mij betekend hebben tijdens het schrijven van dit proefschrift.

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CURRICULUM VITAE

Tjeerd de Boorder was born on June 6th 1975 in Bogotá, Colombia. On the age of five he moved to Zeist in the Netherlands. In 1994 he finished his VWO at de Breul in Zeist and subsequently studied life sciences (biomolecular research and zoology) at the Hogeschool Utrecht from 1994 until 1999. His internship was at the Rudolf Magnus institute. During this period he became more interested in surgical techniques in humans an started the education program for surgical assistant in the St'Antonius hospital in Nieuwegein and finished in 2002. In 2005 he joined the department of Medical Technology and Clinical Physics in the University Medical Center Utrecht under the supervision of Prof. dr. ir. Verdaasdonk. Innovation and clinical support for all surgical specialties played a central role in the activities. He became specialized in the technical aspects of clinical use of energy delivery devices and especially in clinical laser systems. He took the lead in introducing the Thulium laser for different surgical specialties and he started participating in different research projects. In 2014 he started his PhD project which resulted in this thesis. In 2015 he joined the Mechanical Circulatory Support team as a technical Ventricle Assist Device specialist. Currently he is working as a Biomedical Engineer in the UMCU.

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LIST OF ABBREVIATIONS

BPH	Benign Prostatic Hyperplasia
CA	Condylomata acuminata
cm^3	Cubic centimetre
CO_2	Carbon dioxide
CSF	Cerebrospinal Fluid
CW	Continuous Wave
dB (A)	Decibel in A-weighting
dB	Decibel
ENT	Ear Nose and Throat
ENT	Ear Nose and Throat
Er:YAG	Erbium-doped Yttrium Aluminium Garnet
ESD	Endoscopic Submucosal Dissection
ETV	Endoscopic Third Ventriculostomy
f/s	Frames per second
HAART	Highly Active Antiretroviral Therapy
HE	Haematoxylin Eosin
HIV	Human immunodeficiency
Ho:YAG	Holmium Yttrium Aluminium Garnet
HPV	Human papillomavirus
Hz	Hertz
KTP	Potassium Titanyl Phosphate
LA-ETV	Laser-assisted Endoscopic Third Ventriculostomy
LASER	Light Amplification by Stimulated Emission of Radiation
mm	Millimetre
ms	Millisecond
NaCL	Sodium Chloride
Nd:YAG	Neodymium-doped Yttrium Aluminium Garnet
nm	Nanometres
OCT	Optical Coherence Tomography
OH	Hydroxyl group
OR	Operating Room
PND	Pathologic Nipple Discharge
SD	Standard deviation
SNHL	Sensorineural Hearing Loss
ThuLep	Thulium laser enucleation of the prostate
ThuVAP	Thulium laser Vaporisation of the prostate
ThuVARP	Thulium laser Vaporesection of the prostate
ThuVEP	Thulium laser VapoEnucleation of the prostate
TORS	Trans Oral Robotic Surgery
TUR	Transurethral Resection
UMCU	University Medical Centre Utrecht
W	Watt
μs	microsecond