Recent Advances in the Use of Lasers in Otolaryngology

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The laser (Light Amplification by Stimulated Emission of Radiation) has been used in Otolaryngology for over 20 years and is by now an accepted part of the armamentarium. A tremendous amount of work is being done in refining existing techniques and developing new ones, and this review discusses some of the recent advances.

KEY WORDS

Laser, Otolaryngology, Review.

INTRODUCTION

The laser (Light Amplification by Stimulated Emission of Radiation) has been used in Otolaryngology for over 20 years and is by now an accepted part of the armamentarium. A tremendous amount of work is being done in refining existing techniques and developing new ones, and this review discusses some of the recent advances.

BASIC PRINCIPLES

The basic elements of a laser are a lasing medium, an energy source and an optical cavity. The energy is used to elevate the atomic particles of the medium to higher energy states. This situation is called population inversion and acts as a continual source of photons. The excited particless then return to their normal state with the emission of energy in the form of a photon, the wavelength of which is determined by the characteristics of the lasing medium. As the photon encounters another excited elements, it stimulates the release of another photon of the same wavelength, travelling in the same direction and in phase, and in this way the light is amplified. The optical cavity containing the lasing medium has a 100% reflective mirror at one end and a semi-reflective mirror at the other end. The photons travelling along the axis of the mirrors are reflected and thus continue travelling within the optical cavity and stimulating the release of more photons. Photons not travelling along the axis of the mirrors are not repeatedly reflected and are thus not amplified. This reflection produces a temporally and spatially coherent beam of light which escapes via the semi-reflective mirror as the laser beam.

The first lasing medium used was a ruby, but now a number of lasing materials are available, including gas (CO_2, Argon), liquid (the dye lasers), solid (Neodymium : Yttrium Aluminium Garnet and semiconductor diodes) and free electron lasers. Various excitation methods are employed and the laser may be used in continuous wave or various pulsed mode.

TISSUE INTERACTIONS

Laser light falling on tissues may be reflected, scattered, transmitted or absorbed. Only the absorbed light causes a tissue reaction. The main substance absorbing the laser is called the primary chromophore. Absorption produces mainly kinetic excitation of the absorbing molecules. Kinectic excitation produces thermal effects ranging from reversible hyperthermia through enzyme deactivation, protein denaturization and coagulation to dehydration, vaporization and carbonization.

USE OF LASERS

Lasers should be used when they offer a definite advantage over conventional techniques. These advantages may include better haemostasis, improved access to confined areas, improved precision, repeatability, and safety. Lasers in widespread use in Otolaryngology include the CO_2, Argon and KTP/532 laser.

The CO_2 laser has a wavelength of 10.6 µm, in the far infrared. Its main chromophore is water and therefore it has a superficial mode of action, with predictable limited depth of penetration., which makes it a good ablator of tissues. It is however only moderately haemostatic, and commercial fibre-optic transmission is not available although prototype silver halide fibres are being developed.

The Argon laser has a variable wavelength from 488-514 nm. It has an unpredictable depth of penetration which is affected by the presence of char. Its main chromophore is haemoglobin which makes it useful in vascular areas, but it produces greater thermal damage and thus care must be taken to avoid damage to adjacent structures. The beam can be passed down a flexible optical fibre.

The KTP/532 laser has a visible green beam which acts as its own aiming device. It can be used for cutting, coagulation and vaporization, and the beam can be delivered via an optical fibre. Its main chromophore is also haemoglobin.

Mid-infrared lasers are now becoming commercially available. They are based on the YAG crystal which is doped with differing elements that vary the wavelength from approximately 1-3 microns. The advantages of these wavelengths are that they are primarily absorbed by water and are also excellent for bone work. Their high coefficient of absorption and pulsed delivery results in precise tissue ablation and minimal thermal damage.

The main uses of lasers can be divided into therapeutic and diagnostic.

THERAPEUTIC

Lasers have been successfuly used endoscopically for ablating tumours in the respiratory and digestive tract. Other minimally invasive techniques include interstitial laser fibreoptic treatment of head and neck tumours. With the advent of high-speed Magnetic Resonance Imaging, MR guided needle placement for interstitual laser therapy promises further advances[1, 2].

The haemostatis properties of lasers have led to their use in Endonasal Sinus Surgery, where many of the complications are caused by bleeding which limit visibility. The ideal laser for endoscopic sinus surgery should have good haemostasis, good tissue coagulation and ablation, good bone ablation, fibreoptic delivery and the ability to be used in a "wet" field. The CO_2 laser beam has been used endonasally[3] but the beam cannot be delivered via a fibreoptic system, the laser energy is absorbed by blood and water, and the bone interaction is poor. More recently, the CO_2 laser beam has been delivered down a "waveguide" but this is still rather unwieldy. The Argon and KTP/532 lasers have also been used[3], with good surface coagulation of tissue and the ability to pass the beam down a flexible optical fibre, but again bone interaction is poor and soft tissue interaction limited. The Nd:YAG laser can be used intranasally with a contract probe delivery system[4]. Shapshay et al have investigated the in-vitro properties of the Holmium:YAG laser[4] and report good haemostasis, soft tissue and bone ablation. Further evaluation in a clinical setting is uder way.

Helidonis et al[5] have used the CO_2 laser to alter the shape of human nazal septal cartilage without carbonization or ablation of the tissue, and examined the histological changes[6]. This may be beneficial for shaping cartilage grafts, and if the technique can be modified for in vivo use, could have implications for operations such as septorhinoplasty.

Lasers have been used in the treatment of recurrent respiratory papillomatosis, where medical treatments have proved unsuccessful, and the mainstay of treatment has been surgical clearing of the airway with microinstruments or the CO_2, laser, while attempting to minimise scarring. CO_2 laser vaporization has the advantage of being haemostatic for small vessels but there is a risk of thermal damage to underlying normal tissues. Also, char produced during the procedure needs to be suctioned away. Ossof et al[7] reviewed delayed complication rates of CO_2 laser vaporisation and found that removing papilloma from one cord while leaving a cuff of papilloma on the contralateral cord at the anterior comissure produced a lower rate of scarring than removing all papilloma at one attempt. Multiple procedures using this technique would seem to reduce the risk of scarring and glottic webs, but is associated with increased cost and inconvenience to the patient.

The pulsed dye laser at 585 nm has been used successfully to treat cutaneous human papilloma virus lesions. It is thought to selectively destroy the proliferative vasculature underlying the papilloma, and has the potential to produce less pain, scarring bleeding and risk of infection than the CO_2 laser for laryngeal papillomas McMillan et al[8] are currently investigating the effects of the pulsed dye laser (Candela SPTL-1 at 585 nm) on canine vocal cords with a view to clinical treatment of laryngeal papillomatosis.

Laser vaporization for stapedotomy has the advantages of good visualization, a bloodless field, increased precision, and the major advantage of absence of physical contact, reducing the risk of "Floating footplate", and inner ear damage. Ideally, laser energy should be completely absorbed by the stapes footplate, not heat perilymph and not damage inner ear cells[9]. Argon, CO_2 and KTP lasers have been successfully used for stapedotomy. The visible beam lasers such as Argon and KTP do not require a separate aiming beam and their light can be passed down a flexible fibreoptic probe. However, the visible laser wavelength is absorbed mainly by pigmented tissues, and therefore may penetrate the stapes footplate and perilymph to be absorbed by the vessels of the inner ear structures with the associated potential for damage. In contrast, the CO_2 light is absorbed mainly by the footplate or the superficial area of perilymph with less risk of damage to inner ear structures. Perilymph absorption of CO_2 laser light means there is a risk of "boiling" of the perilymph but this can be overcome by pulsing the beam to deliver the energy in very short bursts and limit heating. Lesinski[9] compared the CO_2, Argon and KTP/532 lasers for revision stapedectomies and stapedotomies and concluded that the Argon and KTP lasers possessed better optical characteristics but the CO_2 laser had better tissue characteristics and were safer with regards to the inner ear. Clinically, CO_2 lasers have been used for revision stapedectomy with double the hearing success rate of non-laser techniques with fewer side effects[10].

Segas et al[11] have reported the use of the Excimer laser (wavelength 193 nm) to produce perforations in stapes footplates removed from patients and in cadaver temporal bones. They believe lasers at such wavelengths may be advantageous because of the high absorption of the light in perilymph and thus less risk of damage to the membranous labyrinth. They do not expect any significant increase in temperature of the perilymph because of the small amounts of energy used (100 20mJ pulses) but this remains to be confirmed, and clinical trials have yet to be conducted.

The newer mid-infrared lasers are absorbed by bone and water to a greater extent than the visible wavelength lasers and thus are less likely to damage the inner ear, and unlike CO_2 lasers, they can be delivered down optical fibres. Bottrill et al[12] have investigated in-vitro use of the Thulium:YAG laser (wavelength 2.01 μm) and determined energy parameters for stapedotomy and the thermal effects. The Thulium:YAG laser appears to be a more efficient ablator of bone than the Holmium:YAG laser although the Erbium:YAG laser appears to be even more efficient. The temperature elevation in the experimental setup showed a peak elevation of less than 2°C, lasting less than 1 second, and these compare favourably with other laser systems such as the Argon and KTP lasers which are used clinically to good effect. Acoustic shock damage was not measured in this tudy and needs to be investigatged in further studies.

CO_2 and Nd:YAG lasers at low power have been shown to "weld" tissues together by a process of coagulation, and this process has been successfully for anastomosis of small and large bowel[13], nerves and skin incisions. IndoCyanine Green (ICG) dye mixed with fibrinogen has been used as a solder with a diode laser for microvascular anastomoses[14]. Escudero et al[15] in 1979 reported the successful use of the argon laser to "spot weld" temporalis fascia in seven cases of tympanoplasty. Hanna et al[16] used an animal model to investigate welding of a rat lumbar fascia graft to a lumbar fascia layer in-vitro using an argon ion laser (wavelength 514.5 nm). They found successful welding could be consistently achieved with a laser fluence of 5.1 J/mm^2 and the welded grafts showed a higher tensile strength than controls. The potential advantages in tympanoplasty include less displacement of the graft postoperatively, no need for middle ear packing to support the graft, and anterior "spot-weld" fixation of the graft under the anterior rim of the perforation. This study used a lumbar fascia model, and the contribution of re-epithelialization (an important component of tympanoplasty) or possible adverse effects on re-epitheliazation due to the laser were not assessed. Further studies, using a tympanic membrane model, and clinical trials, comparing laser welded tympanoplasty with conventional procedures are required.

LASER PHOTOTHERAPY

Much research activity has focussed on the field of Laser Phototherapy, which may be further subdivided into PhotoDynamic Therapy (PDT) and PhtoDiagnostic Imaging (PDI)[17]. PDT consists of the interaction between a photosensitizer which concentrates in tumour tissue and laser light of a matching wavelength resulting in a photochemical reaction which damages the tumour tissue. The ideal photosensitizer has the following properties :

1) Easy delivery to site of action, including factors such as absorption for oral compounds, solubility and stability in solution.
2) Selective uptake or selective retention by tumour cells allowing a time window where the photosensitizer is relatively concentrated in tumour tissue with little or none in normal tissue.
3) Photoactivation by laser light of the appropriate wavelength
4) Toxic effect on the tumour cells.
5) Minimal toxicity and morbidity to the host.

A number of agents have been used including Rhodamine, Haematoporphyrin derivatives, Chalcogenapyrilium dyes, Kodak Q-Switch II, Ozazine and Merocyanine dyes. The existence of so many photosensitizers is an indication that no one compound fulfills all these requirements. Biochemical modifications can improve the characteristics of photosensitizers e.g. modifying Kodak Q-Switch Dye to make it soluble in aqueous solution[17]. The basic concepts of PDT and properties of some of the more commonly used laser-dye systems are explored in the excellent review article by Castro et al[17]

Recently, Lipshutz et al[18] report that Carbocyanine dyes demonstrate rapid uptake into tumour cells in-vitro, with good photosensitization using an Argon laser at 488nm, and little sensitivity of the tumour cells to dye alone or laser light alone. These agents require further in-vitro and in vivo assessment. A new compound, Benzoporphyrin Derivative-Monoacid Ring A (BPD-MA) has been developed[19] which absorbs at 690 nm and at this wavelength light penetrates about 1 cm into tissues, compared to the 0.5 cm penetration of light at 630 nm which is used with

Dihaematoporphyrin Ester (DHE). Absorption by haemoglobin and melanin is negligible, thereby maximizing tissue damage. Photosensitivity reactions are much reduced, with any reaction occurring in the first wek as opposed to 4-6 weeks for DHE. It is thought inactivation of the sensitizer occurs in skins, contributing to the reduced skin photosensitivity[20, 21]. Tumour cell retention is similar to DHE but normal tissue clearance is greater, and if these early reports are confirmed this photosensitizer holds great promise for further improvement in photodynamic therapy.

Grant et al[22] report the use of 5-AminoLaevulinic Acid (ALA), a naturally occurring haem precursor, to produce excess Protoporphyrin IX (PPIX), which is an effective photosensitizer. Using 50-100 J/cm^2 of laser light at 630 nm, tumour necrosis of advanced oral squamous carcinoma was induced. The main advantage claimed for this compound is the rapid clearance from tissues within 24 hours, and thus the potential for early repeated courses of treatment. Unfortunately, the data regarding tissue concentration of photosensitizer were only measured in biopsy samples of tumour tissue, and data regarding adjacent normal tissue were unavailable. Clinically, some necrosis of adjacent normal mucosa was seen, and further work is required to determine the optimal dosage and timing of treatment.

Saxton et al[23] have investigated the use of Rhodamine 123 as a photosensitizer for cultured human fibrosarcoma, squamous carcinoma, melanoma and normal fibroblast cells in-vitro. They found uptake was highest for melanoma and fibrosarcoma cells compared to squamous carcinoma or fibroblast cells. However, the photosensitization did not correlate completely with uptake and intracellular concentrations. For example, the fibrosarcoma cells had a lower Rhodamine 123 intracellular concentration than the melanoma cells, but were more sensitive to laser photoinactivation. Also, the normal fibroblasts had double the intracellular dye concentration of the squamous carcinoma cells, but were less sensitive to the photoinactivation. These results indicate factors other than intracellular dye concentration are also important and as further research is performed different photosensitizers may be required to great different tumours most effectively.

Clinically, photodynamic therapy has been used in the treatment of recurrent respiratory papillomatosis, where conventional treatment with microsurgical instruments or laser excision often requires multiple treatments with consequent risk of scarring. Abramson et al[24] describe thirty patients treated with 2.5mg/kg of Dihaematoporphyrin Ether (DHE) as the photosensitizer and 50 J/cm^2 laser energy from an Argon pump dye laser system at 630 nm. They found a significant reduction of about 50% in the rate of papilloma regrowth compared to the previous regrowth rate following conventional clearing with the CO_2 laser. The main side-effect of the treatment was skin photosensitivity. This reduced regrowth rate should translate to reduced number of further treatments with obvious patient and cost benefits. More recently, Abramson et al[25] investigated whether increasing the amount of laser energy from 50 J/cm^2 to 80 J/cm^2 produced any clinical benefit. They found that the higher energy dose did not produce any additional reduction in the rate of regrowth. In fact, two of the patients had increased stridor following treatment with the higher dose and required overnight stay in the Intensive Care Unit for observation. It would seem that further advances will depend on adjusting the dye dosage or characteristics rather than increasing the laser energy.

Heier et al[26] compared the use of PDT using DHE and an Argon pumped dye laser at 630 nm with the Nd:YAG laser alone for the palliative treatment of oesophageal tumours. They found that both techniques achieved luminal patency and relief of dysphagia. The PDT group showed greater increase in dietary performance, Karnofsky performance status and oesophageal grade after one month, and the duration of response was also longer for the PDT group. Other advantages of PDT included reduced damage to normal adjacent tissue because of the relative selectivity, less pain and less smoke obscuring the view during the procedure. However, disadvantages included a waiting time of 1-2 days after injecting the dye before the laser photoactivation, limited depth of tissue penetration, expensive equipment and side-effects such as skin photosensitivity. The duration of photosensitivity was 4-6 weeks, and required precautions or modification of lifestyle in some patients. For these reasons, and the relatively small difference in effectiveness of the two therapies, they recommend reserving PDT for selected cases, for example where the lifestyle would not have to be significantly altered. The next generation of photosensitizers such as Benzoporphyrin Derivative (BPD) may overcome some of these difficulties, for example the rapid clearance from normal tissues allowing earlier laser photoactivation and the reduced skin photosensitivity.

The ability of photodynamic therapy to ablate superficial tumour while being repeatable and minimizing scarring and multilation makes it suitable for the treatment of wide field-change disease such as premalignant and neoplastic disease of the oral cavity. Grant et al[27] report on the treatment of 11 patients with early squamous carcinoma of the oral cavity in association with widespread premalignant disease such as erythroplakia and leukoplakia. Photofrin dye and a copper vapour pumped dye laser (wavelength 630 nm) were used for the photodynamic therapy. Ten out of the eleven patients showed a complete response at 6 to 8 weeks, while one had a patch of mild dysplasia. Follow up at a mean of eleven months showed seven patients had no further premalignant disease, while none of the 11 had any squamous carcinoma at the treated site. Concern has been expressed over the use of radiotherapy for such "field cancerization" disease and photodynamic therapy appears to be a viable alternative, although the inability to penetrate deeply and the side effect of skin photosensitivity need to be considered. The long term effects have yet to be assessed.

PHOTODIAGNOSTIC IMAGING

Photodiagnostic Imaging with lasers may be further subdivided into laser spectroscopy, laser dye fluorescence and dye-conjugated monoclonal antibody imaging[17].

Laser spectroscopy relies on the ability of low power laser light to induce tissue fluorescence without tissue damage. The fluorescent spectrum can then be analyzed spectroscopically and differences between normal and tumour tissues have been detected. Hung et al[28] demonstrated decreased autofluorescence of lung carcinoma using a Krypton Ion laser (wavelength 405 nm) and a Helium-Cadmium laser (wavelength 442 nm). This difference may be related to the relatively high concentrations of oxidised flavins, which fluoresce at 520 nm, in mormal tissues, and the relatively high concentrations of reduced flavins, which do not fluoresce, in tumour tissue. Lam et al[29] used ratio flurometry, measuring the ratio of red to green autofluorescence, to demonstrate the difference between normal and cancerous bronchial tissue. Ratioing can correct for distance, angle and intensity of the excitation light. However, it is not a direct imaging technique and the exact source of the signal cannot be identified. There is also a problem with measuring small early cancers because of the field averaging effect, and if the control site used for calibration also happens to have dysplastic tissue, the results will be false. Harries et al[30] found detectable differences in autoflurescence between carcinoma of the vocal cord and normal vocal cord using the Helium-Cadmium laser. The difference was visible on the monitor image, and confirmed by spectral analysis (although the itensity of the signal did not correlate with the degree of differentiation of the tumour). Two cases are mentioned where this technique proved beneficial in distinguishing recurrent tumour from post-irradiation changes following radiotherapy, where it was difficult to differentiate the two under white light exposure. This technique needs further evaluation with larger numbers of cases to confirm its clinical applications such as evaluation of post radiotherapy larynges and carcinoma in situ.

Lasers may also have a role to play in early detection of oral carcinoma. As the 5 year survival for oral carcinoma is 80% for lesions confined to the mucosa but only 20% if lymph node metastases are present[31], early detction would be very valuable clinically. Ingrams et al[32] have recently conducted in-vitro investigations into the use of Laser Induced Fluorescence (LIF) for detection of oral carcinoma. Their work suggests that LIF is more accurate than clinical diagnosis in detecting early dysplasia. This technique may have a role in screening for oral carcinoma and reducing the number of "normal" biopsies.

Photosensitizers which are selectively taken up or retained by tumour cells can be excited by low power laser light to fluoresce rather than ablate the tumour. Haematoporphyrin and Rhodamine-123 have both been used for this purpose, but the undesirable side effects such as skin photosensitivity have prevented widespread clinical acceptance as an imaging technique.

In recent years the development of monoclonal antibodies targeted at tumour cells and linked to a photosensitizer had promised advances in tumour localization and treatment. The clinical applications of this technique in the field of Otolaryngology have so far been limited, but advances in antibody specificity and antibody-photosensitizer binding may produce therapeutic benefits.

CONCLUSION

The existing uses fo lasers in Otolaryngology are constantly being refined, and new applications of the technology are constantly being developed. Lasers are being developed to produce light at every wavelength, and the development of tunable laser systems means one machine could be used for all wavelengths. Improved light delivery systems are being developed, and new photosensitizers are being produced with more desirable characteristics and fewer side effects. The considerable amount of effort going into research in this field means further advances in the clinical application of laser technology are to be expected.

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