



Review Article

Phonosurgery: A review of current methodologies

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Abstract Cold-steel has served as the gold standard modality of phonosurgery for most of its history. Surgical laser technology has revolutionized this field with its wide use of applications. Additional modalities have also been introduced such as coagulative lasers, photodynamic therapy, and cryotherapy. This review will compare the surgical modalities of cold steel, surgical lasers, phototherapy and cryotherapy. The mechanism of action, tissue effects and typical uses will be addressed for each modality.

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Introduction

Initial forays into laryngology were plagued by the difficulty of accessing the larynx. The first attempts at visualization

were carried out using mirrors which reflected either sunlight or candlelight onto the glottis. The first achievement in visualizing the larynx was successfully carried out in 1829 by Benjamin Babington using his device called a glottiscope.¹

Independently in 1854 the singing teacher Manuel Garcia used a system of mirrors and ambient sunlight to visualize his own larynx during speech and breathing tasks.^{1,2} Ludwig Türck and Johann Czermak are credited with applying these techniques and founding the modern field of laryngology in Vienna in the 1870's.¹

Once laryngeal pathology could be visualized, the next step was the application of steel instruments, namely blades. This led to the first vocal polyp excision by Victor von Bruns in 1862.² Since that time, techniques for visualization of the larynx have dramatically improved. Direct

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visualization of the larynx was made possible by Kerstein in 1895 and later improved upon by Killian with suspension laryngoscopy in 1909.³ Once reliable access to the larynx had been established, further advances in laryngology encompassed the addition of binocular microscopes in the 1970's and decreasing the size of laryngeal instruments to better operate in the confines of the larynx. For the purposes of this paper, this methodology is referred to as cold steel instrumentation. For decades cold steel instruments were the primary methodology used for laryngeal surgery. Lasers were the next significant development with their introduction during the late twentieth century. Soon after, photodynamic therapy and cryotherapy were added to the available methodologies for laryngeal surgery.

This paper explores the numerous modalities available to a laryngologist during surgery. Such modalities include traditional cold steel instrumentation, surgical lasers, photodynamic therapy, and cryotherapy. Surgical lasers are further divided into ablative lasers which encompasses lasers whose main purpose is the ablation of superficial tissue layers and non-ablative lasers whose main purpose is interaction with deeper tissue layers, namely blood vessels. An overview of the mechanism of action, advantages and disadvantages of each of these modalities is provided below. Additionally, the effect each modality has on tissue remodeling and scarring is explored where sufficient quality research exists.

Cold steel instrumentation

Mechanism

The basic mechanism of action of cold steel instrumentation has remained unchanged for centuries. This mechanism entails biomechanical disruption of the laryngeal tissue via shear stress which results in separation of the tissue planes. The simplicity of this mechanism warrants praise in its lack of reliance on technological advancement which contributes to its reliability. However, shear stress is a destructive force in terms of tissue microarchitecture and these destructive effects are examined below.

Tissue effects

Numerous studies have examined the surgical artifacts generated by scalpels versus other cutting methodologies. One such study by Meghana and Ahmedmujib⁴ compared 25 punch biopsies to 25 traditional incisional biopsies for oral mucosal lesions. They found that incisional biopsies were more likely to have histological artifacts such as crush, split, and fragmentation artifacts. Seoane et al⁵ carried out a similar study in a pig model using lingual mucosa punch biopsies compared to incisional biopsies. They also reported increased split artifacts in the incisional biopsy group compared to the punch biopsy group. It is interesting to note that both papers compare incisional and punch biopsies showed differing rates of artifact although both rely on the same mechanism of action for cutting tissue.

Occurrence of histological artifact, while important, may or may not impact the viability of the surgical tissue margins. A tissue specimen may still be viable if these

artifacts do not obscure important factors such as degree of dysplasia or tumor invasion boundaries. A study by Makki et al⁶ sought to compare the effects of cold steel surgical margins versus ultrapulse CO₂ laser surgical margins in laryngeal cancer excision. This prospective randomized study found cold steel to have a significantly lower rate of surgical margins that contained marked artifact or were uninterpretable. Another study by Monteiro et al⁷ compared CO₂ laser, Diode laser, Er:YAG laser, Nd:YAG laser, electrosurgical scalpel and cold scalpel. They examined 130 samples of oral benign fibrous-epithelial hyperplastic lesion excisions. Cold steel was shown to have the lowest rate of artifact in all categories and almost no extension of cellular damage into either the epithelial layer or the connective tissue layer. Additionally, cold steel demonstrated the greatest regularity of incision as rated on a subjective 5-point scale. Finally, Vescovi et al⁸ performed a similar study comparing Nd:YAG laser versus cold steel excision of oral benign fibrous-epithelial hyperplastic lesions. Once again, cold steel showed much lower rates of surgical artifact in all categories.

Ultimately, the above studies demonstrate that cold steel incisions are capable of causing tissue biopsy artifactual changes but do so at a much lower rate compared to laser and electrocautery modalities. It is also important to note that while surgical artifact is prevalent in excisional tissue biopsies of all modalities, the artifacts did not obscure so much as to prevent a pathological diagnosis in almost all cases. This exemplifies the fact that clinical interpretation of the pathological results remains intact as long as the surgical margins are at least 1.5 mm.⁷

Scar formation and its mitigation is of crucial importance in laryngeal surgery. Vocal fold scar formation is triggered by disruption of the vocal fold layered structure.⁹ Such disruptions initiate a cascade of cellular signalling pathways that ultimately result in collagen and elastin reorganization, loss of extracellular matrix components, and decreased vibratory capacity of the vocal fold.¹⁰ Therefore, optimal vocal fold scar outcomes result from the smallest disruption of tissue. Dramatic progress has been made in minimizing tissue damage during laryngeal surgery. Much of this progress can be attributed to more delicate laryngeal instrument design and modification of surgical procedures that mitigate collateral damage to surrounding laryngeal tissue. A recent study compared the effects of a new laser, the picosecond infrared laser (PIRL), with cold steel and electrocautery.¹¹ Each methodology was tested in a mouse dermis model. They found the width and depth of scar formation at three weeks post-incision was greatest for electrocautery. When comparing PIRL and scalpel, there was no statistically significant difference in scar width. However, PIRL did reach significance for estimated scar area, a measurement that includes scar depth, in which PIRL was of smaller area (PIRL scar area mean: 141.46 mm²; 95%CI: 105.8–189.0 mm² versus scalpel area mean: 206.82 mm²; 95%CI: 154.8–276.32 mm²). This study was limited in its measurement of scar formation at 21 days after incision which may not include further scar changes that occur during the remodelling phase of wound healing.

A study by Amini-Nik et al¹² examined the disruptive local tissue effects that occur during use of scalpel and laser. Using a dermal mouse model, they compared linear

scalpel, DELight Er:YAG laser, and PIRL incisions. Results showed typical scalpel wound width ranges from 40 to 120 μm and evidence of extracellular collagen fiber displacement was seen up to 400 μm away from the wound margins. For comparison, the Er:YAG laser demonstrated a maximum wound width of 650 μm and evidence of extracellular collagen fiber displacement up to 800 μm from the wound margin and the PIRL demonstrated maximum a wound width of 8 μm and showed minimal evidence of extracellular collagen fiber displacement. While scar size was not measured in this study, the degree of collagen fiber displacement may act as a surrogate for the degree of scar formation. This reinforces the above studies showing that cold steel instrumentation has significantly less likelihood of forming a scar.

The above studies examining histological changes caused by cold steel were all performed in dermal or oral mucosal models which may not reflect the healing properties of vocal fold epithelium. However, it is clear that cold steel instrumentation has less propensity to cause widespread disruption of the extracellular matrix surrounding an incision in comparison to other surgical modalities. Less disruption leads to decreased extracellular reorganization during healing which ultimately yields less scar formation. This is a major advantage when working on the vocal folds which depend upon vibratory characteristics of the epithelium. Previous papers have utilized technologies used in dermatology and applied them to the vocal folds to decrease scar formation. These technologies have replicated similar results in vocal fold scar formation which indicates similar wound healing processes may be at play in both.^{13–15}

Clinical application

One of the major disadvantages of cold steel laryngeal instruments is the length of the lever arm required to gain access to the larynx. This lever arm is approximately 23 cm long and will accentuate any tremor or instability in the surgeon's hands. Muscle tremor is nearly ubiquitous in all individuals and is augmented via fatigue.^{16–18} Muscle tremor can be mitigated with conscientious body, arm, and instrument positioning but cannot be entirely eliminated without the use of surgical robot instrument stabilization.¹⁹ Conversely, one of the distinct advantages of cold steel laryngeal instrumentation is due to the long lever arm and its direct connection with the working instrument tip which facilitates haptic feedback. The ability to palpate the vocal cords allows the surgeon to surmise the likely etiology of a lesion or estimate the invasion depth of a glottic mass.²⁰ Such intra-procedure evaluation of pathology is critical and may alter how a surgeon approaches a surgical case.

Another disadvantage of cold steel instruments is that they do not possess coagulative properties. Laryngeal surgery is carried out on the small structures of the vocal folds under significant magnification. The small working field can easily be obscured by hemorrhage especially if the laryngeal surgery involves an area of high vascularity such as the vocalis muscle or a large hemorrhagic polyp.²¹ Such deficits can be compensated for with intraoperative use of vasoconstrictive agents such as epinephrine or cocaine solutions.

In certain surgical scenarios, cold steel instrumentation has superior efficacy to other surgical modalities. Zeitels discusses such surgical scenarios in treatment of T1 glottic cancers and benign lesions in several of his papers.^{3,21,22} If the lesion is superficial to the vocal ligament, Zeitels recommends using cold instrumentation to continue the dissection plane along the curvature of the vocal fold by utilizing the long lever arm. If the lesion invades the vocal ligament, the initial dissection down to the vocal ligament should be completed with cold instrumentation. Zeitels then recommends using CO₂ laser to release the lesion from the vocal ligament. A similar hybrid technique is used when the lesion involves the vocalis muscle. As this is a highly vascular area, cold instrumentation is not recommended. Additionally, vocal cord stripping is most easily accomplished using cold instrumentation. Moving forward, it is likely that cold steel instrumentation will never be supplanted by other modalities, but rather act in conjunction to utilize the advantages of each modality.

Lasers

Light Amplification by Stimulated Emission of Radiation, or laser, was first proposed by Albert Einstein in 1917. It was not until years later that the first laser was constructed by Theodore Maiman in 1960.²³ The therapeutic effects of lasers were quickly realized with the first medical use of a laser in the field of ophthalmology for the ablation of a retinal tumor.²⁴ Soon after, Geza Jako used a neodymium-glass laser for laryngeal surgery in dogs.²⁵ The initial lasers used in laryngeal surgery were problematic in their degree of tissue absorption which limited their clinical viability. Further refinement in laser technology led Jako to develop the CO₂ laser which is a commonly used laser in the field of laryngology today.^{26,27}

The basis of laser technology relies upon the stimulated emission of monochromatic, coherent light. A detailed description of these properties is beyond the scope of this paper, but a brief explanation is provided below. Light is composed of particles called photons that move at a constant speed. These particles have properties of both matter and waves which grants them unique applications.²⁸ The monochromatic property of laser light refers to light that is of a single wavelength or color. Fine tuning of the laser wavelength allows selective absorption of the laser energy by the target tissue. The coherent property of laser light refers to the wavelike properties of the light beam in which all emitted photons align both in space and time. These properties account for the achievable precision and high power density of lasers.²⁹

The aforementioned properties of laser light are critical to understanding how lasers can be applied to surgery, but it is how laser light interacts with tissue that determines their efficacy. In order for the laser light to interact with the target tissue, an absorptive tissue element must be present. An absorptive tissue element is a particle that is capable of absorbing a particular wavelength of light. These absorptive tissue elements can be water, melanin, hemoglobin, ink, or any other particle.³⁰ Whether the absorptive tissue element absorbs the light is an inherent property of that particular absorptive element.

When a photon of laser light strikes a tissue surface it has four possible outcomes. First, the photon can be absorbed when it strikes its target absorptive tissue element which generally converts the photon's light energy directly into heat in a process called photothermic effect. This is the primary reason why lasers have the ability to affect their target tissue. Secondly, the photon can reflect off of the tissue and travel in a different direction. Thirdly, the photon can scatter as it interacts with small particles while passing through the tissue. Scatter occurs more frequently with shorter wavelengths of light that are not as capable of diffraction around objects in the photon's path. Finally, the photon can transmit through the tissue if its target absorptive tissue element is not present and thereby not affect the tissue.^{28,31}

Ultimately, the high intensity of laser light in a finely focused beam and its tissue target interaction grants it the ability to ablate tissue.²⁷ The amount of energy absorbed by the target tissue over a given area is termed fluence (measured in J/cm^2).³² Lasers with higher fluence deliver more energy to the target tissue and thus determine how strong of an interaction the laser will have with the target tissue.²⁹ The fluence must be considered with respect to the fluence threshold level for each tissue type which must be exceeded in order to have any physical effect on the tissue. Also, the thermal relaxation time (TRT) of the tissue must be considered in order to avoid excessive surrounding tissue damage. TRT is the time it takes for the tissue to cool to 50% of its peak temperature.³³ This property is important with regard to selecting the pulse rate of the laser beam.³⁰ If the time between laser pulses is less than the TRT, there is minimal transfer of heat to the tissue and no ablation or photocoagulation occurs. Conversely, if the pulse rate is greater than the TRT, heat does not have a chance to dissipate and thereby causes ablation or photocoagulation.²⁹ All of the above factors must be considered as they influence the tissue's exposure to the laser beam and ultimately the rate of destruction of tissue.³⁴

It is important to note the concept of light dispersal over distance travelled or scatter. This effect is small as the coherent property of laser light drastically reduces the laser beam's scatter as it passes through air, yet it does occur due to the laser beam's interaction with air particles. This is highly dependent on the wavelength of the laser light.^{28,29} When this concept is combined with the fact a laser's fluence is directly dependent on area (J/cm^2), the concept of decreasing energy delivered by the laser beam's distance from the target is observed. When the beam's energy falls below the fluence threshold of the target tissue the laser beam no longer has a photothermic effect, but rather can exhibit a photobiomodulation effect. Photobiomodulation typically occurs with red or near-infrared wavelengths as these wavelengths are believed to interact more strongly with proteins involved in the electron transport chain.^{35,36} Photobiomodulation does not physically affect change on the target tissue, but rather stimulates intracellular changes which can have far reaching effects such as cellular metabolic changes, intracellular structural changes, or extracellular remodelling changes to name a few.^{13,29} While this is an exciting new field of application of lasers, further discussion of photobiomodulation is beyond the scope of this paper.

There are many advantages to using lasers in the treatment of laryngeal maladies. The most notable advantage is the hemostatic property of lasers. Lasers typically cause hemostasis due to their photothermic effect which leads to activation of the coagulation cascade. This allows the laryngologist to maintain better visualization of the surgical field. Lasers are also capable of a high degree of precision due to the small spot size generated by the focused beam of light. This is advantageous when working in the small confines of the larynx during surgery. Finally, lasers do not physically come in contact with their target tissue which offers a significant reduction in potential pathogens. This reduction is further enhanced due to the thermal effect of lasers which will inhibit bacterial growth at the surgical site.

One stark disadvantage of the use of lasers in phonosurgery is the risk of airway fire. This is particularly evident with the use of CO_2 lasers³⁷ the incidence of which ranges from 0.4 to 1.5%.^{38–40} CO_2 lasers produce high heat at the area of target interaction. Additionally, the high oxygen concentration of the exhaled air from jet ventilation or air leakage around an insufficiently inflated endotracheal cuff provides an ideal catalyst for combustion. It is important to note that the presence of foreign material is not necessary to cause ignition as discussed in a paper by Stuermer et al.³⁷ In their experimentally controlled conditions, they were able to ignite the smoke plume of the laser while lasering biological tissue without any foreign bodies present. This is an important risk to be considered when using lasers in phonosurgery.

Lasers can be classified as either ablative or non-ablative; traditionally referred to as cutting and photocoagulative respectfully. Some lasers have properties of both depending on the power settings utilized. It is important for a laryngeal surgeon to understand the mechanism behind how these two processes differ and thereby decide in which situations each would be best applied. Each of these categories are discussed below.

Ablative lasers

Mechanism

As with all lasers, ablative lasers derive their effect by interacting with the most superficial layer in which their target absorptive tissue element is present. In the case of ablative lasers, the absorptive tissue element is present in the most superficial of the tissue layers with minimal transmission of energy to deeper layers of tissue. This causes the superficial tissue layers to be ablated thereby exposing deeper layers of tissue to interact with the laser light. Ablation continues if more of the target absorptive tissue element is present in the deeper tissues.

The layer by layer tissue interaction modeled above ideally cuts through the tissue with minimal harm to deeper tissues. However, laser energy is not fully absorbed by the most superficial absorptive tissue element containing layers which allows for some degree of transmission to deeper tissues. Additionally, heat is transferred from the site of laser-tissue interaction via conductive effects. These effects contribute to the thermal penetration depth, or degree of heat transfer to surrounding tissues, which varies between lasers and with tissue properties.⁴¹ Thermal depth

can be minimized by taking the TRT of the tissue into account and adjusting the power settings to minimize surrounding tissue heat effects.

Lasers

The most common ablative laser utilized in laryngology is the CO₂ laser. This laser produces a high powered beam of infrared light ranging from 9300 to 10,600 nm. Water acts as the primary absorptive tissue element for these wavelengths of light. Water is present in all tissues and contributes to the CO₂ laser's large degree of versatility. Traditionally, the CO₂ laser's major disadvantage was that it required transmission through a rigid optical tube via mirror and lens assemblies. This limited the CO₂ laser to use with microscopic procedures in which direct line of sight could be achieved with the target tissue. In recent years, however, the development of a quartz flexible waveguide eliminated this drawback.^{42,43}

Another ablative laser used in laryngeal surgery is the thulium doped yttrium-aluminum-garnet laser (thul:YAG).^{26,27,44} This laser produces an infrared beam similar to CO₂ but at 2013 nm wavelength. Water again acts as the primary absorptive tissue element at this wavelength.⁴⁵ This laser has similar scope to the CO₂ laser except the thul:YAG laser can be transmitted via glass flexible waveguide. This introduces the ability to perform endoscopic procedures both in the OR and in office settings.

A recently developed ablative laser, the picosecond infrared laser (PIRL), shows promising results in preliminary studies in its application to laryngeal surgery. The PIRL is rapidly pulsed at durations as short as 100 ps with a wavelength of 2960 nm which acts upon water as its primary absorptive tissue element. Contrary to other lasers, the PIRL has a narrow ablative radius of 10–30 μm with very minimal surrounding tissue damage.⁴⁶ The PIRL has a narrow ablative radius which shows less scarring and thermal damage when compared to other laser surgical methods when examined histologically. These effects may contribute to better vocal outcomes.^{47,48} The PIRL shows promise as a newer and less destructive ablative laser if these results can be translated to clinical application.

Tissue effects

Ablative lasers are designed to have powerful effects, and as such, are more likely to cause surrounding tissue damage. The degree to which the surrounding tissue is affected depends mainly on the power settings of the laser used. This makes direct comparison of studies difficult due to differing parameters. However, broad conclusions can be drawn with regard to ablative lasers. A multitude of studies examined the gross and histological effects of the CO₂ laser in comparison to scalpel incisions in a dermis model.^{49–53} They showed the CO₂ laser had extension of thermal effects outside of the incision with noticeable alteration to the extracellular collagen, increased inflammatory reaction, and faster epithelial wound migration. These effects ultimately led to increased fibrotic tissue after the primary wound healing phase. The use of cooling techniques such as forced air cooling have been shown to reduce the gross tissue changes surrounding the incision for certain power settings.⁵⁴ Fewer studies exist examining histologic tissue effects of the thulium laser, however, one study showed

more significant thermal effects at the wound margins in a subjective comparison of CO₂ and thulium lasers.⁴⁴

In addition to the scarring and wound healing effects of ablative lasers, these higher powered lasers have a tendency to cause eschar formation or carbonization of tissue. Generally, once the tissue reaches temperatures above 100 °C the tissue, the tissue carbonizes and turns a black color.^{26,29} The carbonizing effect varies depending on laser type and power settings. CO₂ lasers used in continuous mode have the highest propensity for carbonization. The carbonized tissue must be frequently removed using a damp gauze to maintain adequate surgical exposure.

Again, it is important to point out that the above studies used mostly dermis models which are a different tissue type and architecture compared to the vocal folds. Therefore, direct comparison is not possible with respect to scarring and remodeling.

Clinical uses

Although ablative lasers have significant thermal effects that can damage the delicate layered structure of the vocal fold, they still serve an important role in laryngology. Ablative lasers are best suited for large lesions that require significant debulking with the added advantage of hemostasis. This allows significant tissue removal without copious bleeding which maintains adequate surgical exposure. Diseases in which ablative lasers prove useful include anterior glottic webs, granulomas, and significant recurrent respiratory papillomatosis.⁵⁵ Additionally, ablative lasers have been used in oncologic resection such as T1 and T2 laryngeal tumors to great effect.^{56,57}

Non-ablative lasers

Mechanism

The non-ablative laser's primary goal is to achieve hemostasis of blood vessels in the target tissue. This is accomplished by utilizing hemoglobin as the primary absorptive tissue element for these lasers. The superficial tissue layers of the vocal fold are devoid of hemoglobin which thereby allows transmission of the majority of the laser energy through the superficial tissue layers to interact with the deeper blood vessels. However, if an incorrect amount of energy is delivered to the blood vessel, the vessel can rupture rather than coagulate.⁵⁴ With this model, the epithelium and lamina propria overlying the blood vessel can be preserved and thereby preserves vocal function.

Lasers

The primary non-ablative laser used in laryngology is the potassium-titanyl-phosphorous (KTP) laser. This laser generates 532 nm light which is part of the green spectrum of light.⁵⁸ This wavelength is highly absorbed by hemoglobin and melanin and minimally absorbed by water.⁵⁴ The KTP laser is typically used in a gated continuous wave mode which effectively creates rapid pulses which minimizes thermal injury to surrounding tissue. Additionally, the KTP laser can be transmitted via flexible waveguide to the target tissue. If the flexible waveguide is maintained at a distance of several millimeters from the target tissue, the laser demonstrates non-ablative effects. If the optical fiber

tip is brought near contact or outright contact with the target tissue, the laser demonstrates ablative effects.⁵⁹ This is due to the scattering effect of air discussed previously. The ablative effect is due to high concentration of heat generated at the fiber tip which has an effect similar to electrocautery. This results in carbonization of the tissue as well as build up of carbonization on the fiber tip which must be removed if further photoangiolytic non-contact mode is desired at a later stage.

The first laser designed for non-ablative effect was the pulsed-dye laser (PDL). As suggested by the name, this laser generates pulsed light at a wavelength of 585 nm. This wavelength is also absorbed by hemoglobin and has similar non-ablative effects to the KTP laser.⁶⁰ However, KTP lasers have replaced PDL in laryngeal surgery due to superior hemostasis with KTP lasers and the ability to greatly vary the pulse settings of the KTP laser.⁶¹ Also, PDL are more expensive due to their solid state optical resonator and must be delivered through a larger diameter flexible waveguide as compared to a KTP laser.⁶²

A newer laser has recently emerged called the blue light laser. This laser generates light at 445 nm which is highly selective for hemoglobin.⁶³ The authors in Hess et al state many advantages of this new laser. Namely, its ability to act as both a non-ablative laser and an ablative laser. They state equivalent non-ablative effects when compared with the KTP laser when using lower energy settings. In near-contact mode with higher energy settings the laser is capable of ablating tissue with minimal carbonization and minimal visible surrounding tissue effects. Finally, the laser is cheaper, has a small footprint, and utilizes flexible waveguides of 300–400 μm diameter. The authors state clinical efficacy in several cases involving ectatic vessels, recurrent respiratory papillomatosis, Reinke's edema, polyps, contact granuloma, and other benign lesions both in office and in the operating room. There is a lack of further literature exploring tissue effects and optimal energy settings for this laser, but the results look promising thus far.

Tissue effects

Non-ablative lasers direct their energy at coagulating blood vessels as opposed to removing tissue. Their selective use of hemoglobin as an absorptive tissue element helps to minimize the surrounding tissue effects. Therefore, it can be challenging to determine the degree of energy transfer to the target tissue. A system was created by Mallur et al⁶⁴ to quantify this energy transfer based on visual changes which was then validated by seven academic laryngologists. Even with a visual scale, the study demonstrated the reviewers had difficulty distinguishing between non-contact and contact tissue end effects. This is likely attributable to the fact that the tissue end effects commonly associated with contact of the optical fiber with the tissue (charring and ablative changes) can be achieved with higher energy settings in non-contact modes and vice versa.

Far fewer studies have examined the histological changes of non-ablative lasers in comparison to ablative lasers or cold steel. A study by Eigsti et al⁵⁹ examined several tissue biopsies from a single individual with recurrent respiratory papillomatosis. They demonstrated

histologic changes as expected with corresponding levels of the KTP scale proposed by Mallur et al. Another study by Zhang et al⁶⁵ showed KTP laser treatment after vocal fold injury via punch biopsy led to decreased inflammatory biomarkers and collagen transcription levels. This implies the KTP laser may have photobiomodulatory effects that influence wound healing.

Clinical uses

Non-ablative lasers are much newer in their application to the field of laryngology. Even so, they have already proven useful in many different areas. Their use in early glottic cancers such as T1 glottic carcinoma have been demonstrated.^{66,67} This is mainly due to the fact tumors tend to be highly vascularized due to release of angiogenic factors which makes them amenable to the laser's photo-coagulative effects. Non-ablative lasers have diminished efficacy at debulking large tumors and are better suited to treatment of small, superficial lesions of the larynx due to their non-ablative properties. Also, due to the minimal scarring of non-ablative lasers, they have shown efficacy for treatment of other laryngeal disorders such as Reinke's edema, laryngeal papillomas, and hemorrhagic polyp resection.^{60,68–70}

Photodynamic therapy

Mechanism

Recently, researchers have begun investigating the efficacy of using photodynamic therapy (PDT) to treat laryngeal disease. PDT works by introducing a photosensitizer (PS) into diseased tissues which acts as an exogenous absorptive tissue element. However, a major difference exists between the lasers-absorptive-tissue-element interaction described above and that of the absorptive tissue elements used in PDT. Most lasers utilize an absorptive tissue element that undergoes a photothermic reaction in which the absorptive tissue element's specific wavelength of light is converted to heat energy. In the case of PDT, the absorptive tissue element typically undergoes a photochemical reaction in which reactive oxygen species are generated upon activation by its specific wavelength of light.^{71,72} Reactive oxygen species then interact with various cellular biomolecules which interrupt homeostatic cellular function or interfere with critical cellular structures whose effects eventually lead to the demise of the cell.⁷³

PDT has a significant advantage over traditional laser therapy in that PDT can be targeted to a specific tissue type or cellular type. Only the specific site in which the absorptive tissue element was introduced will be affected by the therapy. Selection of the type of absorptive tissue element and ensuring its specific uptake by the desired cell adds a further layer of bioengineering complexity to this treatment modality. Various routes of administration of PDT absorptive tissue elements have been explored such as topical, oral, local injection, or systemic administration.⁷¹ Additionally, many different compounds have been explored such as porphyrin, chlorins, phthalocyanines, and porphycenes.⁷¹ To date, none have demonstrated ideal application and concentration in the desired tissue.

Tissue effects

PDT carries out its tissue effects via inducing intracellular chemical reactions as described above. If enough intracellular changes occur, this results in several possibilities of cell death. First is apoptosis in which the cell undergoes programmed cellular demise. The second is necrosis in which the cell rapidly releases intracellular contents and induces an inflammatory reaction. Finally, the cell can undergo autophagy-associated cell death in which the cell consumes its own intracellular contents effectively cleansing the cell.⁷⁴ All of these mechanisms result in tissue death which then sloughs off or is broken down by phagocytic immune cells.

The selective nature of PDT serves as a major advantage for using this emerging therapy. This makes it ideal for use in removing only diseased tissue. However, a disadvantage of PDT is that it is not capable of ablative action to remove superficial tissue layers thereby exposing deeper layers of diseased tissue to the effects of PDT. Because of this drawback, PS activation is limited to depths of 2–10 mm depending on the PS utilized.^{74,75} This can be overcome with multiple treatments spaced far enough apart to allow the superficial tissue layers to be removed or can be performed on the wound bed after the bulk of the lesion has been removed by another modality.⁷⁴

Clinical uses

PDT is an emerging treatment method in early stage laryngeal cancers. Freche et al⁷⁶ published an early study examining 32 patients with T1 carcinomas of the vocal folds. They found that 78% of the patients had complete tumor regression and were free of any recurrences two months post-operatively. A later study by Biel looked at 276 patients with T1 to T3 all with N0 laryngeal tumors and found a five year cure rate of 91% after a single treatment of PDT.⁷⁷ Finally, a study by Franco examined eight patients with laryngeal leukoplakia and found a 78% reduction in size of the lesions following PDT.⁷⁸

The above studies exemplify the efficacy of PDT when utilized for treatment of uncomplicated early stage laryngeal cancer or precancerous lesions but do not examine voice outcomes pre and post-PDT. It has also been shown that PDT leads to minimal amounts of scarring, a crucial factor in voice outcomes.⁷⁹ However, there are few studies that encompassed voice outcomes. One study led by von Beckerath et al⁸⁰ looked at voice quality post PDT treatment of laryngeal cancer using a subjective pre and post-PDT assessment performed by a phonometrist. They found that there was no reduction in vocal quality after PDT with 50% having improved voice following PDT. Another study by Biel⁸¹ showed subjective improvement in voice in all patients treated for T1 to T3 laryngeal tumors as rated by the study team. Further research using objective voice measures is warranted to determine PDT's efficacy as a voice sparing procedure.

Cryotherapy

Mechanism

The medical applications of cold have been in use for thousands of years, dating back to the ancient Egyptians use of cold for its anti-inflammatory properties.⁸² It continues to be a popular method of treatment with high potential due to its healing properties. In recent years, cryotherapy has been applied to laryngeal surgery as an adjuvant therapy to laser surgery. Cryotherapy consists of using a cryogen, often liquid nitrogen, to apply extreme cold to a target area.⁸³ Cryotherapy uses a cryoprobe which acts as an applicator through which the cryogen is delivered to the target site. Liquid nitrogen is currently the most common choice of cryogen due to its minimum achievable temperature (−197 °C) being appropriate for benign and malignant lesions.⁸² Cryotherapy achieves its tissue destructive effects by using extreme cold to damage blood vessels and capillaries in the target area leading to ischemia and eventually tissue necrosis.⁸³ The formation of ice crystals also occurs, which creates an osmotic gradient that draws water extracellularly and leads to cell rupture. Typically, cryotherapy consists of multiple freeze–thaw cycles. The length and target temperature of these cycles depends on the tissue type and whether cell target cells are benign or cancerous.⁸³ Multiple sessions of cryotherapy may be necessary depending on the type of the lesion.

As with any surgical technique, cryotherapy requires careful attention to several factors in order to achieve acceptable surgical outcomes. The first consideration regards isotherms or the spherical area surrounding the site of application.⁸³ The effects of extreme cold spreads throughout the tissue from the center of application with an equal radius in all directions. Surgeons must have adequate knowledge regarding the properties of isotherms in the target tissue to accurately achieve the target temperature. Another important factor to consider is that air has low thermal conductivity. This limits the cryoprobe's effectiveness as its distance from the target area increases.⁸³ Finally, no excised tissue remains after cryotherapy which limits determination of adequate surgical margins.⁸³

Tissue effects

The primary value of cryotherapy stems from its excellent healing properties, resulting in minimal scarring and desirable postoperative voice quality.⁸² Because scarring is the primary cause of poor postoperative voice quality, cryotherapy's potential to produce minimal scarring yields high potential as a treatment for laryngeal lesions. Gong et al¹⁵ found that cryotherapy in a rabbit model simulates an environment similar to that of the fetal wound-healing environment, which is characterized by minimal inflammation, rapid re-epithelialization, and reduced collagen formation. Knott et al⁸⁴ found both reduced collagen

formation with more organized structure after application of cryotherapy, along with decreased keratinization. Another study by Li et al⁸⁵ investigated differences in healing of skin wounds caused by burn and freeze injuries. It was found that a burn wound contained three times the amount of collagen as normal skin, and the freeze wound contained $\frac{3}{4}$ as much collagen as normal skin. The reduced formation of collagen is crucial to the preservation of postoperative voice quality. Due to its minimal scarring and positive postoperative voice outcomes, cryotherapy has the potential to become an important treatment for laryngeal diseases such as papilloma, glottic carcinoma, and both glottic and subglottic stenosis.^{86–88}

Cryotherapy has a wide range of clinical applications for laryngeal surgery involving the treatment of laryngeal cancers as well benign laryngeal lesions. A 1968 study by Gage⁸⁹ used cryotherapy on 50 patients with oral or oropharyngeal cancer and showed comparable survival rates to surgical excision. Further advancement of cryotherapy has led to its use as an adjuvant to laser surgery. A 2006 study by Knott et al⁸⁷ on early-stage glottic cancer demonstrated that endoscopic laser laryngeal surgery with adjuvant cryotherapy not only yielded excellent primary site control of the cancer, but also led to subjective and objective improvements in postoperative voice quality. In this study they administered cryotherapy to the wound margins after excision of the tumor by CO₂ laser and after confirmation of wound margins via frozen-section.

Although emphasis has been placed on cryotherapy as a treatment for laryngeal cancer, several studies address the success of the use of cryotherapy as a treatment for papillomatosis.^{86,90}

Cryotherapy has the potential to be a medical treatment for laryngeal diseases resulting in minimal scarring and optimal postoperative voice quality and is therefore an important topic for future research. For one, future research should continue to look at the healing process of cryotherapy, exploring the healing environment produced and how it results in minimal scarring. Future research should also aim to explore how the use of cryotherapy could apply to other laryngeal diseases beyond cancer, while collecting more quantitative data regarding postoperative voice quality.

Conclusion

Laryngologists today are faced with a difficult decision regarding treatment methods of laryngeal diseases. Through development of new technology and techniques, methods such as cold steel instrumentation, laser excision, photodynamic therapy, and cryotherapy must all be considered when deciding what is best for the patient. With each method having unique advantages and disadvantages, it is important for surgeons to have knowledge of each technique and its suitability for the situation at hand. Additionally, combinations of the above methods allow for mitigation of certain complications while preserving the overall benefits. Further advancement in cold instrumentation, laser technology, phototherapy, and cryotherapy

will continue to refine the field of laryngology to improve outcomes while minimizing complications.

Declaration of competing interest

None.

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