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Comparison of Ho:YAG Versus Nd:YAG Thoracoscopic Laser Treatment of Pulmonary Bullae in a Rabbit Model

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ABSTRACT

Objective: To determine the relative efficacy and morbidity of Ho:YAG versus Nd:YAG laser treatment of bullous lung disease in an animal model. **Summary Background Data:** Laser coagulation procedures for treatment of emphysematous pulmonary bullae and heterogenous emphysema continue to evolve. The role of lasers in lung volume reduction surgery remains controversial due to issues of relative efficacy and morbidity. The Nd:YAG laser is most commonly used for these procedures. We hypothesized that the shallower penetration of the Ho:YAG laser may be better suited for laser bullae coagulation and emphysema lung volume reduction with increased efficacy and reduced lung injury. **Methods:** Thirty New Zealand White rabbits (15 normal rabbits; 15 with bullous lung disease) were evaluated with Ho:YAG compared to Nd:YAG laser exposures. Bullae were coagulated by either Ho:YAG or Nd:YAG treatment. In all animals (bullous-induced and normals), unaffected lung tissue in the upper lobes and contralateral lungs were treated with 5 spot exposures of Nd:YAG and Ho:YAG, each to assess depth of lung injury. Animals were sacrificed at Days 0, 7, and 21 and their lungs were examined histologically. **Results:** Ho:YAG and Nd:YAG exposures caused equivalent lung injury to normal lung tissue. In the acute phase, parenchymal necrosis depth was similar for both Ho:YAG and Nd:YAG ($850 \pm 273 \mu\text{m}$ vs. $900 \pm 270 \mu\text{m}$ respectively, $p = 0.7$). By Day 7, lung necrosis depth was $925 \pm 133 \mu\text{m}$ Ho:YAG vs. $1225 \pm 235 \mu\text{m}$ Nd:YAG ($p = 0.33$), and lung fibrosis depth was $300 \pm 134 \mu\text{m}$ Ho:YAG vs. $558 \pm 127 \mu\text{m}$ Nd:YAG ($p = 0.11$). By Day 21, pulmonary parenchymal necrosis was not seen. Pleural fibrosis depth was maximal at Day 21, reaching $250 \pm 102 \mu\text{m}$ for Ho:YAG vs. $300 \pm 156 \mu\text{m}$ Nd:YAG ($P = 0.88$). Pleural necrosis depth was $67 \pm 42 \mu\text{m}$ Ho:YAG vs. $48 \pm 34 \mu\text{m}$ Nd:YAG ($p = 0.42$) on Day 7 and resolved by Day 21. During surgical coagulation procedures, the Ho:YAG laser was dramatically more efficient in coagulating bullae. The Ho:YAG laser required less exposure at equivalent power and resulted in immediate desiccation of bullae, in sharp contrast to the Nd:YAG laser. **Conclusions:** Because the Ho:YAG was more effective and did not result in more acute lung injury than the standard Nd:YAG laser in this study, Ho:YAG lasers may have improved potential for laser treatment of bullae or lung volume reduction surgery (LVRS) compared to Nd:YAG lasers.

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INTRODUCTION

Lung volume reduction surgery for emphysema and treatment of emphysematous pulmonary bullae has been described using a variety of surgical methods including lung stapling, laser removal of bullae, and a combination of both techniques.¹⁻⁸ Whereas stapling procedures may be more effective than Nd:YAG LVRS in some presentations,^{2,5,6,8,9} the exact role of lasers in coagulating bullae has not been clearly determined.^{7,10} The Nd:YAG laser is the most commonly reported laser for this surgery. However, laser-induced lung injury after laser treatment has been found.^{1,11-13} Late adverse effects from laser lung reduction procedures include an increased incidence of delayed pneumothorax.^{1,6,14,15} Thus, we continue to investigate new laser approaches at different operating wavelengths and characteristics to improve current techniques of laser-assisted lung volume reduction surgery.

In this study, we investigate Holmium:Yttrium-Aluminum-Garnet (Ho:YAG) laser treatment of emphysematous pulmonary bullae. This laser has been used in other medical applications but has not been widely reported for lung surgery. The Ho:YAG laser used in these studies operates in the pulsed mode at a wavelength of 2.1 microns in the near infrared region with strong water absorption peaks. Given these operating characteristics, we hypothesize that the Ho:YAG laser would be more efficient at ablating bullae and coagulating lung tissue while resulting in less lung tissue damage.

METHODS

Animal approval

This protocol was approved by the UC Irvine institutional AALAC certified review board in compliance with State, Federal, and Institutional regulations.

Study design

Fifteen male New Zealand White (NZW) rabbits (3–5 kg) underwent induction of bullous emphysema using intratracheal carrageenan and intravenous Sephadex beads, according to previously published methods.¹¹ The induction of bullae involved instillation of carrageenan into the airways following IV injection of Sephadex beads. Male albino rabbits (3–4 kg) were injected with 0.35 ml of 10 mg/ml Sephadex G-50 beads (100–300 μ m diameter, Pharmacia, Uppsala, Sweden) suspended in physiologic saline via marginal ear vein. Three hr after injection of Sephadex beads, rabbits were anesthetized using inhaled Isoflurane 5%, followed by 0.2 cc Ketamine/Xylazine in a 1:1 mixture via IV injection. Rabbits were intubated with a 21-gauge guidewire under direct laryngoscopic visualization using a #1 straight blade laryngoscope and placed in a right lateral decubitus position. A 12-gauge, 12-inch catheter was inserted over the guidewire into the trachea and passed until wedged. A right-sided directional guidewire was used to increase likelihood of right mainstem intubation. The catheter was then withdrawn 1–2 cm. Ten milliliters of heat sterilized (15 min, steam autoclave treated 250°F, 15 psi) 0.75% carrageenan (lambda carrageenan #4, Sigma Chemical Co., St.

Louis, MO) solution in physiologic saline were injected into the wedged bronchial catheter. The catheter was removed and the rabbit monitored for adequate respiratory function.

These 15 rabbits underwent diagnostic thoracoscopy at a 6-week timeframe following carrageenan exposure. Eleven of the rabbits developed emphysematous bullae to various degrees. The Ho:YAG laser was used to ablate one portion of a bulla and Nd:YAG laser was used to ablate another portion of the bulla or another bullae (when multiple bullae formed). Animals were sacrificed at Day 0, 7, and 21 post laser exposure.

Thoracoscopy

Operative techniques have been previously described¹¹ Anesthesia was induced in the rabbits with 2:1 Ketamine HCl (100 mg/ml):Xylazine (20 mg/ml) 0.75 cc/kg IM. Animals were intubated with a 3.0 mm to 3.5 mm noncuffed endotracheal tube. Oxygen saturation (Ohmeda Biox 3700 Pulse Oximeter, BOC Health Care, Madison, WI), end tidal CO₂ (Ohmeda 5200 CO₂ Monitor, BOC Health Care, Madison, WI), and EKG (Hewlett Packard 78353B Continuous EKG Temperature Probe Monitor, BioMedical Services, Palo Alto, CA) were monitored continuously. Rabbits were shaved, sterilely prepped with Nolvasan scrub, draped, and placed on ventilatory support using a Harvard Ventilator (Harvard Apparatus Dual Phase Control Respiratory Pump-Canine, Harvard Co., South Natick, MA) with initial settings: 50 ml tidal volume, 35% inspiratory time, rate 20–40 bpm, adjusted to maintain end tidal CO₂ 35–40 torr. Hypothermia was prevented with a surgical warming pad. A 25-gauge IV catheter was placed in a marginal ear vein and lactated Ringers solution was infused at 5–15 cc/h.

Animals were placed in a left lateral decubitus position. Under sterile conditions, three small 5-mm thoracoscopy trocars were placed intercostally (apical, diaphragmatic, and anterior) to allow full visualization and access to the lung surface. The lung surface was then carefully visualized for evidence of bullae formation.

FIG. 1. Thoracoscopic view of bullous lesion in rabbit.

FIG. 2. Histologic section of multiple small bullous lesions in rabbit lung. Inflammatory changes are also seen in interstitial areas.

Laser treatment of non-bullous lungs

For Ho:YAG treatments, a Trimedyn Omnipulse Holmium Laser (Trimedyn Inc., Irvine, CA) was used. It was operated at 2100 nm, delivered by a 0.55-mm core diameter 3 meter length silica fiber (Holmium Bare Fiber) operated in a free beam mode. The laser settings were five Watts pulsed at ten Hertz with a pulse duration of 350 μ sec (duty cycle of 0.035%), peak power of 1428 W, and a resultant power density of 160–250 W/cm². The spot size was 2.5–3 mm at the lung surface, with the fiber tip held approximately 7–9 mm from the surface. Fiber delivery was calibrated daily prior to use. Five spot exposures were performed on non-bullous lung tissue with Ho:YAG laser to determine the depth and quality of laser-induced lung injury. The duration of treatment to each spot was 2 sec.

For Nd:YAG treatments (Laserscope KTP/Nd:YAG laser, operating at 1064 nm, Laserscope Surgical Laser Systems, San Jose, CA), a 0.4 mm core diameter plastic-clad silica multi-mode optical fiber (Endostat 0.4 mm $\times$ 12 ft, #0010-0622, San Jose, CA) with a flat cut end was used in a free beam mode. Again, a power density of 160–250 W/cm² was applied by using a 5-Watt delivered continuous beam with a 2.5–3 mm diameter spot size at the lung surface (approximately 7–9 mm from

the fiber tip). The position and movement of the delivery fiber was manually controlled to maintain a constant distance from the fiber tip to the lung surface. Fiber delivery was calibrated daily, prior to use. Duration of treatment for each laser spot was 2 sec.

Rabbits were disconnected from the ventilator during laser exposure to prevent lung movement variability. Inspired oxygen concentration was decreased to 21% during laser exposures to avoid risk of combustion.

Laser treatment of bullous lungs

Bullae were coagulated using either Ho:YAG or Nd:YAG lasers at the same settings listed above. Bullae were exposed repeatedly until fully coagulated and contracted. In animals with single, large bulla, portions of bulla were treated with one laser, with the remaining portion treated with the other laser. Response of the bullae to laser coagulation were assessed subjectively because there was a dramatic difference between Ho:YAG and Nd:YAG effectiveness.

Following laser exposure, a 12 Fr. neonatal chest tube was placed percutaneously, sutured in place, and initially connected to suction (20 cm H₂O). The skin was sutured with 2-0 silk. After the lung was re-expanded, the chest tube was connected to a Heimlich valve.

Post-operatively, the rabbits were monitored and extubated. Rabbits were placed in restraining jackets. The chest tube and jackets were removed later that same day. Rabbits were placed in a standard holding pen. On postoperative Days 1, 2, and 3, the animals received prophylactic doses of Combiotic (0.35 cc).

Histologic preparation

All animals were anesthetized with high doses of Ketamine HCl/Xylazine intramuscularly. One thousand units of heparin were injected intravenously. Two cc Eutha 6 were administered intravenously and the descending aorta was severed for exsanguination. The lungs and heart were removed en-block. Following necropsy, the lung was inflated by intratracheal instillation of 10% formaldehyde in phosphate buffered solution at 25-cm water pressure for at least 24 h. The lung was sliced sagittally at 0.2–0.4 cm thickness. Lung sections were processed routinely

FIG. 3. Histologic section of Nd:YAG laser-induced pulmonary parenchymal injury in normal rabbit lung.

FIG. 4. Histologic section of Ho:YAG laser-induced pulmonary parenchymal injury in normal rabbit lung.

TABLE 1. Nd:YAG VERSUS Ho:YAG EXPOSURE OF NON-BULLOUS LUNG

	Pleura				Lung parenchyma			
	Necrosis		Fibrosis		Necrosis		Fibrosis	
	Ho:YAG	Nd:YAG	Ho:YAG	Nd:YAG	Ho:YAG	Nd:YAG	Ho:YAG	Nd:YAG
Acute	0	0	50 ± 26	30 ± 21	850 ± 273	900 ± 270	0	0
Day 7	67 ± 42	48 ± 34	58.3 ± 36	158.3 ± 52	925 ± 133	1225 ± 235	300 ± 134	558.3 ± 127
Day 21	0	0	250 ± 102	300 ± 156	0	0	66.7 ± 42	33.3 ± 24

Depth of injury (M ± SEM) in microns. All *p* values are nonsignificant between Ho:YAG and Nd:YAG laser exposure injury depth (*p* values >0.05 by unpaired *t*-test).

and embedded in paraffin. Seven micron thick sections were stained with hematoxylin and eosin (H&E) and studied by light microscopy.

Coded histopathologic specimens were reviewed by a pathologist who was blinded to clinical data as previously described.^{12,16} The pathological changes observed in the pleura and lung following the laser treatments were layered or in zones, with the changes deepest in the center of the lesion and tapering toward the periphery. With a scale inserted in the eyepiece of the light microscope, the depth of changes was measured in the deepest central position of the lesion, perpendicular to the pleural surface.

RESULTS

Visual observations

With the Ho:YAG laser, bullae contracted extremely quickly. The visceral pleural surface would rapidly contract, coagulate, and desiccate. In general, it would only take 2 to 5 sec to obliterate a large (e.g., 1–2 cm) bulla. This was in stark contrast to the Nd:YAG laser. With the Nd:YAG laser, very little acute effect was evident even with prolonged (>30-sec) exposures. This was particularly evident in thin-walled, relatively translucent bullae.

While the histologic depth of injury in normal lung tissue was reasonably similar with both lasers, the qualitative appearance during surgery was distinct. Ho:YAG exposures caused immediately visible coagulation and contraction of tissue evident on the lung surface. In contrast, Nd:YAG treatment caused subtle blanching, minimal contraction, and what appeared to be subpleural-surface effects. It was difficult to visualize any effects of the laser on the pleural surface and effects appear delayed. With Nd:YAG treatment, lung would usually become hyperemic before slowly shrinking in size with tissue coagulation.

Histologic results

As noted in our previous study,⁹ several semi-distinct zones of lung damage were noted after laser treatment to the external lung surface. There is an evolution from acute lung edema and congestion to necrosis, and finally, fibrosis.

Acutely, a zone of hemorrhage, necrosis, and congestion was observed in the lung parenchyma. The depth of lung necrosis was 850 ± 273 microns with the Ho:YAG laser compared to 900 ± 270 microns (ns, $p = 0.7$) (Table 1). Interestingly, no significant necrosis was seen at the pleural surface. At Day 7, however, necrosis, hemorrhage, and congestion were seen in the pleura and in the lung parenchyma, as well as chronic inflammation and fibrosis (Table 1). The depth of pleural and parenchymal necrosis was statistically similar for Ho:YAG and Nd:YAG lasers. The depth of pleural fibrosis was negligible at this time. The depth of lung fibrosis was not significantly different, though there was a trend toward increased depth of injury with the Nd:YAG laser (Table 1).

By Day 21, the acute injury and necrosis had resolved, while fibrosis and chronic inflammation remained. There was similar degrees of pleural and parenchymal thickening for both lasers.

The total depth of fibrotic changes was relatively shallow by this time.

DISCUSSION

Laser applications for treatment of pulmonary diseases continue to expand. Surgical approaches for management of pulmonary emphysema have recently been developed including video-assisted thoracoscopic lung staple and laser volume reduction surgery.^{1–8} The Nd:YAG laser remains the most commonly used laser for this purpose. However, there is substantial debate of the value of lasers, either as primary or adjunctive treatment, in this procedure.^{2,6,7,8,10} Improved laser settings and techniques that may minimize lung injury while optimizing clinical results are needed to improve the utility of lasers in LVRS and other pulmonary surgical applications.

In previous studies^{12,16} Nd:YAG, CO₂, and various pulsed modes have been investigated to determine possible methods for minimizing lung injury. However, no clear advantages were found for CO₂ or Nd:YAG in pulsed or continuous modes. In our present study, we examined the depth of injury of the Ho:YAG laser on bullous lung tissue, a laser which has not been previously reported in this clinical setting in comparison with commonly used Nd:YAG lasers.

The degree of acute lung injury appeared to be similar for both the Ho:YAG and Nd:YAG lasers by histopathology. The depth of injury was comparable to what has been previously described with the Nd:YAG laser.^{9,10} At Day 7, resolution of the acute injury began with pleural involvement seen and the start of lung fibrosis. The depth of injury in the lung parenchyma was not significantly deeper for the Nd:YAG than Ho:YAG laser. In bullous tissue, signs of acute and chronic damage in the underlying lung parenchyma had virtually resolved by Day 21 and pleural fibrosis at the parenchymal surface remained. Again, there was no significant difference between the two lasers in the degree of pleural fibrosis. We speculate that the inflated bullae increased the distance to the lung parenchyma and may also have acted as a thermal insulator, thus minimizing the degree of long lasting thermal damage to the underlying lung tissue which would lead to fibrosis.

There may also be differences in tissue interactions with the Ho:YAG versus Nd:YAG lasers in lung tissue. Ho:YAG has a longer wavelength than the Nd:YAG laser and greater water absorption that leads to a shallower depth penetration. Absorption is less dependent on hemoglobin than Nd:YAG. We have previously shown in this rabbit bullae model that inflated pulmonary bullae have minimal perfusion using Doppler measurements.¹⁷ This may explain the ineffectiveness of Nd:YAG coagulation of thin-walled bullae.

There are other issues that need further investigation. Total laser exposure time for coagulation of the bullae was not controlled for in this study. The Ho:YAG laser coagulated bullae much more rapidly than the Nd:YAG laser. Had the exposure time been controlled, different depths of lung injury in the underlying tissue may have resulted if both lasers were administered to bullae for equal amounts of time. However, the relevance of such results would be difficult to interpret, as desired clinical endpoint is effective bullae coagulation, and not equivalent joules used. Nonetheless, it was clear, subjectively, that

the Ho:YAG laser was much more effective than the Nd:YAG for bullae coagulation.

In this study, we compared the Ho:YAG laser to Nd:YAG laser effectiveness. The carbon dioxide laser was not investigated. In general, Ho:YAG laser properties are very similar to CO₂ laser clinical effects. However, the Ho:YAG laser has distinct advantages in delivery systems because it does not require an articulating arm and can be delivered through flexible fiber systems.

Because the Ho:YAG laser appears to coagulate bullae in a more effective manner than the Nd:YAG laser without causing increased lung injury, it appears that the Ho:YAG may have improved potential for treatment of pulmonary bullae or laser LVRS. The areas of ablation by the Ho:YAG are easily visible, facilitating clinical use. Experiments using different power settings and pulse frequencies need to be performed with the Ho:YAG laser in an attempt to find optimal settings in balancing lung injury with clinical efficacy. It appears that the Ho:YAG laser is worthy of further investigations.

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