

Better safe than sorry? Results from an ex-vivo study demonstrate that the thulium fiber laser may cause eye injury without standard protection

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Abstract

Introduction: We conducted a study using an ex-vivo porcine model to evaluate whether a thulium fiber laser (TFL) induces ocular injury in the context of inadvertent exposure to the laser beam.

Methods: A 365 µm TFL was positioned at a set distance (0 cm, 5 cm, 8 cm, and 10 cm) from a freshly harvested (<12 hours) porcine eyeball and the laser was activated for one second at select laser settings for lithotripsy (0.2 J at 50 Hz, 0.5 J at 20 Hz, and 1 J at 10 Hz) and soft tissue ablation (2 J at 10 Hz, 1 J at 50 Hz). The experiment was repeated with laser safety goggles and prescription eyeglasses. Thermal injury was assessed by histopathological analysis.

Results: Without eye protection, corneal injury was observed even at 10 cm away for one lithotripsy setting (1 J at 10 Hz) and both tissue ablation settings. All thermal injuries observed were superficial only, except for at 0 cm distance, where deep-layer injury was observed. Laser safety goggles offered complete protection regardless of setting or distance. Partial protection was demonstrated with prescription glasses: histopathological damage was observed for both soft tissue ablation settings and only at 0 cm for two lithotripsy settings (0.5 J at 20 Hz, 1 J at 10 Hz).

Conclusions: The TFL can induce ocular injury at close distances and at higher power settings. The use of laser safety goggles confers complete protection while prescription eyeglasses confer partial protection. Further study is warranted.

KEY MESSAGES

- Inadvertent firing of the novel thulium fiber laser at short distances and higher energy settings may result in superficial corneal injury.
- Wearing laser safety goggles confers complete protection while prescription eyeglasses offer partial protection.

Introduction

The holmium:YAG laser (Ho:YAG) has been the gold standard for endourological procedures for the past two decades and was a significant improvement compared to its predecessors with respect to safety and efficacy.¹⁻³ Its settings for treatment effectiveness, as well as eye safety have previously been elucidated.⁴⁻⁹

In recent years, advancements in laser technology have given rise to the thulium fiber laser (TFL). Preliminary data suggest that the TFL demonstrates equally effective and even superior capability to Ho:YAG. Its advantages over Ho:YAG include, but are not limited to, a higher water absorption coefficient that is associated with higher energy absorption and lower ablation thresholds, an ability to house thinner laser fibers enabling greater intraoperative access and manipulation, easier storage and maintenance, as well as increased capability of working at higher frequencies with lower pulse energy.^{10,11}

With the advent of TFL, it is crucial to delineate eye safety guidelines for clinical use. Using an ex-vivo pig eye model, we sought to determine the distances and pulse energy settings at which the TFL may induce ocular injury in the event of inadvertent exposure in the operating room. In addition, we tested the efficacy of laser safety goggles and prescription eyeglasses in preventing TFL-induced injury.

Methods

The study was conducted in a laboratory of the medical engineering department at the University Health Network - Toronto General Hospital site (TGH). A 365 μm TFL was used with the SOLTIVE™ SuperPulsed Laser System (Olympus Corporation, Westborough, MA, U.S.) for all experimental trials; this fiber size was selected as it allowed for both lithotripsy and tissue ablation settings.

The pig eye — an ex-vivo model

The pig eye was selected as an ex-vivo animal model for evaluating potential harmful effects of accidental TFL exposure to human eyes. Pig eyes share many anatomical similarities with human eyes^{12,13} and have previously been used as a model of Ho:YAG-induced injury by Villa et al.⁷

The pig eyeballs were obtained from a nearby abattoir. All animals were sacrificed on the same day the study took place, with eyeballs being kept in 0.9% NaCl isotonic solution at room temperature between procurement and testing (<12-hour interval) in order to preserve tissue moisture and integrity.

Protocol and equipment

A total of 65 pig eyeballs were used in the study: 60 experimental and five controls. For each experimental trial, an eyeball was placed in an ocular globe holder (Figure 1A). The tip of the TFL was securely positioned at a set distance from the eyeball, pointing towards the center of the cornea (Figure 1B). Twenty eyeballs were exposed to the TFL beam from different distances (i.e., 0 cm, 5 cm, 8 cm, and 10 cm) using varying pulse energy settings: three settings that are clinically relevant to lithotripsy (i.e., 0.2 J at 50 Hz long pulse, 0.5 J at 20 Hz long pulse, and 1 J at 10 Hz short pulse) and two settings that are relevant to soft tissue ablation (2 J at 10 Hz short pulse and 1 J at 50 Hz long pulse). Based on the study by Villa et al,⁷ and the assumption that accidental exposure to the TFL beam in an operative setting would last no longer than a fraction of a second, the TFL was activated for one second for each pulse energy-distance pairing. This protocol was repeated using 20 eyeballs with laser safety goggles (Part #015.T0006.00, LaserVision, MN, U.S.) and 20 eyeballs with prescription eyeglasses (single-vision lens, -4.0 spherical). For trials with safety goggles and eyeglasses, distances were measured from the surface of the lens of goggles or eyeglasses rather than the cornea, and the lens was positioned at a distance of 0.75 cm from eyeballs in order to mimic natural eyewear conditions.

Prior to TFL testing, the UltraPulse CO₂ laser (Lumenis, San Jose, CA, U.S.) was used to mark the cornea peripheries of each eyeball at a setting of 4 W with in-plane lines measuring 2 mm in length and depth. This was done in

order to more accurately target the center of the pupil with the TFL beam and to delineate the plane for histological sectioning (Figure 1C). These markings were made far away from the center of laser exposure. Three additional eyeballs were marked with the CO₂ laser but not tested with the TFL (CO₂ controls), and two eyeballs were neither marked with the CO₂ laser nor tested with the TFL (normal controls).

The ocular globe holder prototype was acquired from www.thingiverse.com (design by Dennis Humphrey) and subsequently customized using the Prusa Slicer software and Prusa i3 MK3S 3D printer (Prusa Research, Prague, Czech Republic). Polylactic acid 1.75 mm material was used for 3D printing. Adjustable handles were made with metallic pins and 3/8 x 1/8 x 1/8 inch rare-earth ring magnets (Lee Valley Tools Ltd., Scarborough, ON, Canada). The TFL was reliably activated for one second with the help of the Denkovi™ relay switchboard (Denkovi Assembly Electronics, Bulgaria), a custom-made Python script, and a pedal actuator that consisted of a solenoid driven lever and a set of weights (Figure 1D).

Pilot study

A pilot study (n=5) using the aforementioned laser settings was conducted for histopathological analysis of relevant eye structures, including the cornea, lens, retina, and optic nerve.

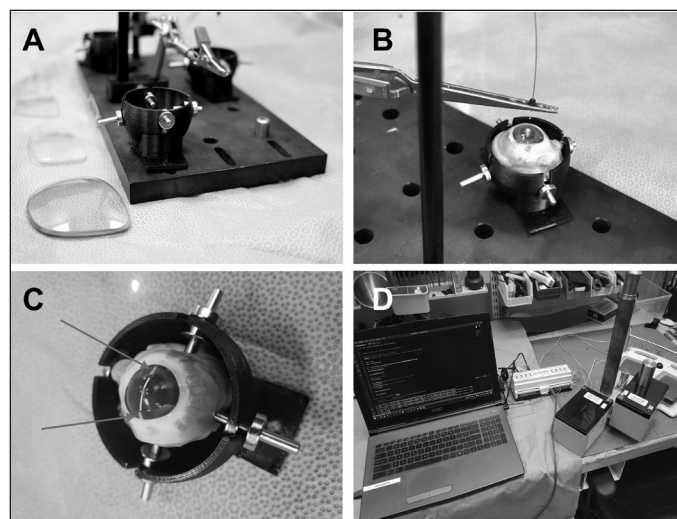


Figure 1. Experimental design and setup. **(A)** For each trial, an eyeball was placed in a 3D printed ocular holder and held in position by adjustable handles. **(B)** Using pliers, the tip of the thulium fiber laser was securely positioned at a set distance (i.e. 0 cm, 5 cm, 8 cm, or 10 cm) from the eyeball and pointed towards the center of the pupil, after which the laser was activated for 1 second at select laser settings for lithotripsy (i.e., 0.2 J at 50 Hz long pulse, 0.5 J at 20 Hz long pulse, and 1 J at 10 Hz short pulse) and soft tissue ablation (2 J at 10 Hz short pulse and 1 J at 50 Hz long pulse) without protection, with laser safety goggles, and with prescription eyeglasses. **(C)** Prior to laser testing, the UltraPulse CO₂ laser was used to mark the iris peripheries of each eyeball (red arrows) in order to more accurately target the center of the pupil with the laser beam (purple asterisk) and to delineate the plane for histological sectioning (green line). **(D)** A custom-made Python script and a pedal actuator were used to accurately and reliability activate the laser for one second.

Tissue processing and histological evaluation

Immediately after the experimental trial or designation as control, each eyeball was examined grossly for signs of injury and fixed in 10% neutral buffered formalin solution (Sigma-Aldrich, St. Louis, MO, U.S.). All specimens were submitted within 12 hours to the Pathology Research Program at our institution, where they were grossed, embedded in paraffin, sectioned at 5 microns, and stained using hematoxylin-eosin (H&E). Two anatomical pathology residents at the University of Toronto with experience in ophthalmic pathology (AG and TS), independently evaluated stained slides from all specimens for histopathological evidence of injury to the cornea, lens, retina, and optic nerve. In a vast majority of cases, there was initial consensus between the two reviewers. Final consensus was achieved by reviewing the discordant results when needed.

Results

From our pilot study, there were no histopathological findings in the lens, retina, and optic nerve that differed significantly between eyeballs belonging to the experimental group vs. control groups. Consequently, the results focus on corneal injury. The histopathological findings are summarized in Supplementary Table 1 (available at cuaj.ca) and Tables 1, 2.

Figure 2A shows a representative H&E section of a normal control cornea without laser injury, whereas Figure 2B

depicts a section of a CO₂ control without injury. A variety of histopathological abnormalities were observed in the cornea in experimental trials: distorted and streaming epithelial nuclei, homogenization of the stroma with eosinophilic changes, vacuolar condensation of the epithelium and stroma, and full thickness perforation. TFL-induced thermal injuries to the cornea were classified as follows: superficial burn lesion (<50% of the corneal thickness) (Figure 2C), deep burn lesion (>50% of the corneal thickness) (Figure 2D), and necrotic features (seen as the darker pink area adjacent to the burn lesion in Figure 2C and surrounding the burn lesion in Figure 2D).

As shown in Supplementary Table 1 (available at cuaj.ca), there was no histopathological evidence of thermal injury to the cornea in normal controls. Likewise, eyeballs with CO₂ marking only (CO₂ controls) did not exhibit any injuries that would have confounded experimental trials.

For eyeballs exposed to the TFL without protection at lithotripsy settings, superficial burn lesion and necrotic features were observed for 0.2 J at 50 Hz within 8 cm, for 0.5 J at 20 Hz within 5 cm, and for 1 J at 10 Hz within 10 cm (albeit without necrotic features), while deep burn lesion was observed only for 0.2 J at 10 Hz and for 0.5 J at 20 Hz from 0 cm away (Table 1).

Findings were less varied for tissue ablation settings: superficial burn lesion and necrotic features were noted even at 10 cm for both 2 J at 10 Hz and 1 J at 50 Hz, while deep

Table 1. Histopathological findings in the cornea of pig eyes exposed to a 365 µm TFL for 1 second without protection

Clinical indication	Experimental condition		Histopathological finding in the cornea		
	TFL setting (power)	Distance from cornea	Necrotic features	Superficial burn lesion	Deep burn lesion
Lithotripsy	0.2 J, 50 Hz (10 W)	0 cm	X	X	X
		5 cm	X	X	
		8 cm	X	X	
		10 cm			
	0.5 J, 20 Hz (10 W)	0 cm	X	X	
		5 cm	X	X	
		8 cm			
		10 cm			
	1 J, 10Hz (10 W)	0 cm	X	X	
		5 cm	X	X	
		8 cm	X	X	
		10 cm		X	
Soft tissue ablation	2 J, 10 Hz (20 W)	0 cm	X	X	X
		5 cm	X	X	
		8 cm	X	X	
		10 cm	X	X	
	1 J, 50 Hz (50 W)	0 cm	X	X	X
		5 cm	X	X	
		8 cm	X	X	
		10 cm	X	X	

Cells marked with "X" indicate presence histopathological injury whereas cells without marking represent absence of injury. Power (measured in W) = energy (J) x frequency (Hz). TFL: thulium fiber laser.

Table 2. Histopathological findings in the cornea of pig eyes exposed to a 365 µm TFL for 1 second with prescription eyeglasses

Clinical indication	Experimental condition		Histopathological finding in the cornea		
	TFL setting (power)	Distance from cornea	Necrotic features	Superficial burn lesion	Deep burn lesion
Lithotripsy	0.2 J, 50 Hz (10 W)	0 cm			
		5 cm			
		8 cm			
		10 cm			
	0.5 J, 20 Hz (10 W)	0 cm	X	X	
		5 cm			
		8 cm			
		10 cm			
	1 J, 10Hz (10 W)	0 cm	X	X	
		5 cm			
		8 cm			
		10 cm			
Soft tissue ablation	2 J, 10 Hz (20 W)	0 cm	X	X	
		5 cm	X	X	
		8 cm			
		10 cm			
	1 J, 50 Hz (50 W)	0 cm*			
		5 cm	X	X	
		8 cm	X	X	
		10 cm	X	X	

Cells marked with "X" indicate presence histopathological injury whereas cells without marking represent absence of injury. Power (measured in W) = energy (J) x frequency (Hz). *Aberrant finding, likely related to pathological processing error. TFL: thulium fiber laser.

burn lesion was seen only from 0 cm away for these two settings (Table 1). No histopathological effects were observed in the cornea of eyeballs exposed to the TFL with laser safety goggles from any distance or at any pulse energy setting. Table 2 shows results for eyeballs exposed to the TFL with prescription eyeglasses. Although the results suggest that the TFL causes superficial burn lesion and necrotic features for 2 J at 10 Hz within 5 cm and for 1 J at 50 Hz within 10 cm (soft tissue ablation settings), eyeglasses appear to confer meaningful protection for lithotripsy settings: superficial burn lesion and necrotic features were seen only for 0.5 J at 10 Hz and 1 J at 10 Hz from 0 cm away — a distance at which inadvertent exposure to the laser beam is unlikely to occur. No eyeballs incurred deep burn lesion at any laser setting from any distance with eyeglasses. Both laser safety goggles (Supplementary Figure 1A; available at cuaj.ca) and prescription eyeglasses (Supplementary Figure 1B; available at cuaj.ca) were visibly damaged by the TFL beam during the study.

Discussion

Eye injuries were reported to account for approximately 28% of all adverse events resulting from the use of lasers in urology according to a study examining decades-long records of two prominent databases.⁹ However, no eye injuries were associated with the Ho:YAG laser. This finding undermines

the blanket mandate put forth by certain authoritative bodies and laser manufacturers stipulating that safety goggles be used for all laser operations.^{2,7,8,14} In fact, in an ex-vivo model assessing the safety of Ho:YAG on pig eyes, Villa et

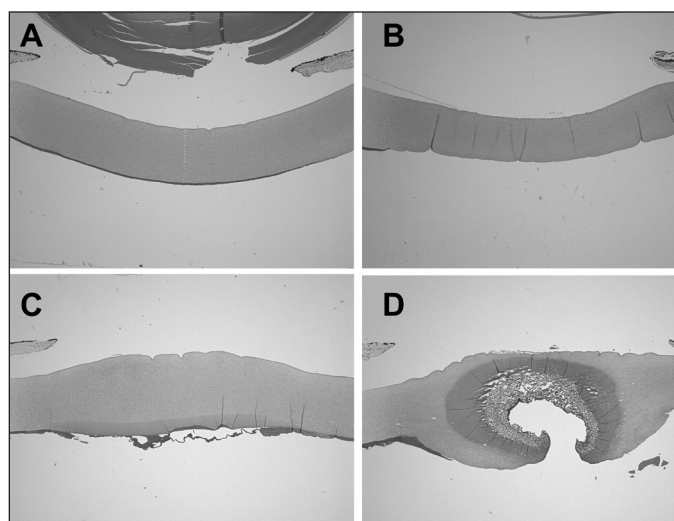


Figure 2. Representative hematein-eosin sections of the cornea after thulium fiber laser-induced thermal injuries at 1.6x magnification factor. (A) Normal control without laser injury. (B) CO₂ control without laser injury. (C) Superficial burn lesion (<50% of the corneal thickness). (D) Deep burn lesion (>50% of the corneal thickness).

al found there to be no damage to eyes when the laser was placed at a distance of at least 5 cm away from the cornea, and prescription eyeglasses were found to be as protective as laser safety goggles at all laser settings and distances.⁷

Given the rapid adoption and use of TFL in endourological procedures, we used the pig eye as an ex-vivo model to elucidate the distances and pulse energy settings at which inadvertent exposure to the TFL beam might result in ocular injury. We found evidence of histopathological damage corresponding to exposure even at 10 cm away from the cornea for one lithotripsy setting (i.e., 1 J at 10 Hz) and two soft tissue ablation settings (i.e., 2 J at 10 Hz and 1 J at 50 Hz). No histopathological damage was observed in eyeballs exposed to the TFL with safety goggles from any distance or at any pulse energy setting, thus confirming the efficacy of goggle protection for TFL. It is important to note, however, that at 0 cm, visible marking from the TFL was seen on laser safety goggles even at the lowest energy setting (i.e., 0.2 J at 50 Hz). Prescription eyeglasses have been purported to confer adequate protection from Ho:YAG laser injury; however, in our study, we found they were only partially protective, mainly for lithotripsy settings and at distances 5 cm or further. Higher power settings often used for tissue ablation were associated with injury even at further distances.

Compared to the Ho:YAG study by Villa et al,⁷ our study of the TFL demonstrated significantly more corneal damage, even at distances of 10 cm for some settings. This may be due to the TFL's higher tissue absorption coefficient ($\mu_a=129.2 \text{ cm}^{-1}$ at $\lambda=1940 \text{ nm}$ vs. $\mu_a=28 \text{ cm}^{-1}$ at $\lambda=2100 \text{ nm}$ for Ho:YAG), which would result in greater energy absorption by cells.^{15,16} Another explanation could relate to differences in the storage and handling conditions of pig eyeballs between tissue harvesting and testing. Shortening the duration between harvesting and testing, and keeping eyeballs immersed in 0.9% NaCl isotonic solution, would have preserved natural moisture and hence water particle availability for laser energy absorption.

Two aberrant findings in our study warrant attention. First, we observed at least some degree of epithelial loss in 54 experimental specimens (90%), as well as in one normal control (50%) and three CO₂ controls (100%). As such, it was not interpreted as TFL-induced thermal injury but as an artefact. Epithelial loss most likely occurred during tissue processing or fixation.^{17,18} Second, no injury was recorded for 1 J at 50 Hz from 0 cm away with prescription eyeglasses. This would be biologically impossible given that injuries were observed for lower power settings at the same distance and at all other distances for the same setting. Moreover, this eyeball had grossly visible injury after laser exposure and the laser beam burned through the eyeglasses completely. The most probable explanation for this data is that the injury was not captured properly during tissue processing.

It is important to note that although our results indicate the possibility of TFL-induced ocular damage without laser

safety goggle protection, these findings should be interpreted in the clinical perspective: the probability of the laser fiber breaking during surgery and the beam hitting the eye from a sufficiently short distance remains presumably low.

One potential limitation of our study relates to the use of a single laser fiber size. In theory, variations in total power (wattage), and to a lesser degree energy and rate settings, would have the most impact on thermal injury. At consistent laser settings, the laser fiber size should not affect thermal damage related to laser beam exposure. As such, we feel fiber size alone likely has limited impact on the outcomes of the study. Another potential limitation was that only a single eyeball was used to evaluate each setting and distance. While a power calculation cannot be performed for this type of study design, the trend and pattern of damage seen in our study suggests additional eyeballs would unlikely change the results significantly. We did not assess every potential laser setting possible with the Soltive™ TFL so cannot comment on alternate TFL settings used clinically, but feel the data does provide a frame of reference for clinicians. Finally, we did not evaluate the impact of pulse duration on tissue damage so cannot comment on how this variable impacts potential ocular tissue injury in relation to various TFL settings.

To the best of our knowledge, this is the first study to assess eye safety with TFL use. Unique aspects of our study include the incorporation of 3D printed models and computer programming for maximizing consistency among experimental trials and minimizing potential confounders. Also, the study was conducted on the same day as the animals were sacrificed and the eyeballs were kept in isotonic solution in order to minimize the impact of post-mortem tissue disintegration. Finally, in addition to routine laser lithotripsy settings, we tested two tissue ablation settings (e.g., for thulium laser enucleation of the prostate) for broader impact and readership.

Conclusions

Unlike Ho:YAG, which has previously been shown to induce no ocular damage beyond 5 cm away from the cornea in an ex-vivo pig eye model, the results of our study indicate that the TFL can induce corneal injury even at a 10 cm distance for certain settings. Our study also confirms that while prescription eyeglasses offer some protection against TFL-induced injury, they may be inadequate protection for high power settings. Though the likelihood of accidental TFL firing in the operating room, under the specific controlled settings of our study, is highly unlikely, the potential for corneal injury does exist without laser safety goggles. Further study is warranted.

Competing interests: The authors do not report any competing personal or financial interests related to this work.

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This paper has been peer-reviewed.

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