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in vitro ureter model

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Abstract. Using a validated in vitro ureter model for laser lithotripsy, the performance of an experimental thulium fiber laser (TFL) was studied and compared to the clinical gold standard holmium:YAG laser. The holmium laser (\(\lambda = 1908\) nm) was operated with standard parameters of 600 mJ, 350 \(\mu\)s, 6 Hz, and 270-\(\mu\)m-core optical fiber. The TFL (\(\lambda = 2120\) nm) was operated with 35 mJ, 500 \(\mu\)s, 150 to 500 Hz, and a 100-\(\mu\)m-core fiber. Urinary stones (60% calcium oxalate monohydrate/40% calcium phosphate) of uniform mass and diameter (4 to 5 mm) were laser ablated with fibers through a flexible video-ureteroscope under saline irrigation with flow rates of 22.7 and 13.7 ml/min for the TFL and holmium laser, respectively. The temperature 3 mm from the tube’s center and 1 mm above the mesh sieve was measured by a thermocouple and recorded throughout each experiment for both lasers. Total laser and operation times were recorded once all stone fragments passed through a 1.5-mm sieve. The holmium laser time measured \(167 \pm 41\) s (\(n = 12\)). TFL times measured \(111 \pm 49\), \(39 \pm 11\), and \(23 \pm 4\) s, for pulse rates of 150, 300, and 500 Hz, respectively (\(n = 12\) each). Mean peak saline irrigation temperatures reached \(24 \pm 1^\circ\)C for holmium, and \(33 \pm 3^\circ\)C, \(33 \pm 7^\circ\)C, and \(39 \pm 6^\circ\)C, for TFL at pulse rates of 150, 300, and 500 Hz, respectively. To avoid thermal buildup and provide a sufficient safety margin, TFL lithotripsy should be performed with pulse rates below 500 Hz and/or increased saline irrigation rates. The TFL rapidly fragmented kidney stones due in part to its high pulse rate, high power density, high average power, and observation of reduced stone retropropulsion and may provide a clinical alternative to the conventional holmium laser for lithotripsy. © 2014 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JBO.19.12.128001]

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1 Introduction

Kidney stone disease is a common and costly disorder that affects about 10% of the US population. Each year, over 3 million patient visits to health care providers occur with over 500,000 treatments in emergency rooms for kidney stones. Annual costs to the national health care system are estimated to be $5.3 billion. Furthermore, over the last two decades, a significant increase in stone disease has been associated with changing demographics, diet, and lifestyle. On the basis of demographic and lifestyle modeling, continued and further increasing rates of stone disease are expected to occur in the coming decades.

A significant percentage of kidney stone cases requires surgical intervention. Holmium:YAG laser lithotripsy via advanced ureteroscopy has become a major technique for minimally invasive destruction of urinary stones. For small to moderate sized or multiple stones, holmium laser lithotripsy has even become the preferred surgical option over extracorporeal shock wave lithotripsy. Maximal clinical efficiency of laser lithotripsy is important to decrease operation time, surgical risk, and costs.

Over the past decade, our research group has been studying the thulium fiber laser (TFL) as an alternative lithotripter to the holmium laser. We have recently observed that TFL kidney stone ablation rates scale linearly with pulse rate, and when operated at high pulse rates up to 500 Hz, the TFL is capable of rapid stone ablation. However, these previous studies did not take into account stone retropropulsion or active saline irrigation during the procedure, and there was also no direct comparison with the conventional holmium laser, currently the gold standard laser lithotripter in the clinic. The objective of this study was, therefore, twofold: (a) to compare TFL and holmium laser times and total operation times necessary to fragment similar stones in an in vitro ureter model, and (b) to record saline temperatures near the stone sample in order to provide feedback on safety margins for potential future clinical application.

2 Methods

2.1 Thulium Fiber Laser Parameters

A 100-W experimental TFL (TLR 110-1908, IPG Photonics, Oxford, Massachusetts) with a center wavelength of 1908 nm was used in these studies. This wavelength was chosen to closely match a high-temperature water absorption peak in tissue in the infrared spectrum. The continuous-wave TFL was electronically modulated using a function generator (DS345, Stanford Research Systems, Sunnyvale, California) to operate in long-pulse mode, producing 500-\(\mu\)s pulses for lithotripsy studies, similar to conventional holmium laser pulse lengths of 350 to 700 \(\mu\)s. The TFL produced an approximately
Gaussian, near single-mode beam profile, originating from an 18-μm-core thulium-doped silica fiber, with a built-in collimator providing a 5.0-mm-diameter output beam. A 25-mm-focal-length calcium fluoride lens was used to focus the TFL beam down to a $1/e^2$ spot diameter of $\sim 25$ μm for coupling into a standard, disposable, low-hydroxyl, 100-μm-core silica optical fiber (AFS105/125, Thorlabs, Newton, New Jersey). All stone ablation experiments were performed with a TFL output pulse energy of 35 mJ, pulse duration of 500 μs, and variable pulse rates of 150, 300, or 500 Hz.

### 2.2 Holmium:YAG Laser Parameters

A 20-W, clinical holmium:YAG laser (Medilas H20, Dornier MedTech, Wessling, Germany) with a center wavelength of 2100 nm was used in these studies for direct comparison with the TFL. The holmium laser was used with a standard 270-μm-core clinical, low-OH silica optical fiber (RFID Holmium Lightguide, Dornier MedTech). The laser was operated with standard clinical parameters, including a pulse energy of 600 mJ, pulse duration of 350 μs, and pulse rate of 6 Hz. Laser pulse energy was measured using a pyroelectric detector (ED-200, Gentec, Canada) connected to an energy/power meter (EPM1000, Molectron, Portland, Oregon).

### 2.3 Urinary Stone Samples

All stone samples were composed of 60% calcium oxalate monohydrate and 40% calcium phosphate (Fig. 1). These stones were chosen because calcium oxalate stones are common and comprise about 80% of all stone compositions encountered in the clinic. All of the stone samples originated from a single patient, had a consistent mass (40 to 100 mg) and size (4 to 5-mm diameter) and were available in large quantities. Stone samples were desiccated in an oven for 15 min and then weighed with an analytical balance (Model AB54-S, Mettler-Toledo, Columbus, Ohio) before lithotripsy experiments to determine their initial mass. Stone samples were then placed in the ureter model, immersed in a saline bath and experiments were conducted immediately upon rehydration. A total of 12 stone samples were used for each set of laser parameters.

### 2.4 Experimental Setup

A 6-mm-inner-diameter tube with an integrated 1.5-mm mesh sieve and microthermocouple was used as a simple in vitro ureter model in these studies (Fig. 2). Kidney stones were placed inside of the tube and rested on the sieve, with the entire ureter model submerged in a saline bath. The distal tip of a flexible digital video-ureteroscope (URF-V, Olympus, Southborough, Massachusetts) was then placed inside the tube. The optical fiber was inserted through the 3.6 Fr (1.2 mm) single working channel of the ureteroscope and positioned in contact with the urinary stone sample under magnification. Constant saline irrigation at room temperature (22°C) was provided by a saline bag elevated 100 cm above the experimental setup. Saline flow rates through the ureteroscope working channel with the 100-μm-core [244-μm-outer diameter (OD)] TFL and 270-μm-core (464-μm-OD) holmium laser fibers measured 22.7 and 13.5 ml/min, respectively. It should be noted that there is always continuous saline irrigation during endoscopic laser lithotripsy in the clinic, primarily to clear stone dust and maintain visibility of the stone in the surgical field during the procedure. All stone samples were free to move around inside the ureter model during the...
studies. An experienced, practicing urologist (P.I.) performed all of the laser lithotripsy experiments. The stone sample was irradiated with the laser until all ablated fragments were sufficiently small (<1.5-mm diameter) to pass through the mesh of the sieve. Total laser times and operation times were recorded for each experiment. “Laser time” was defined as the total time that the laser was on. “Operation time” was defined as the total time from laser initiation until the final stone fragments passed through the sieve, including both laser time and any additional time used to re-adjust the fiber position or clear the visual field when the laser was momentarily not in use. Videos of each stone ablation experiment were also recorded for subsequent analysis.

2.5 Thermocouple Temperature Measurements
Temperature monitoring was performed during all experiments. An insulated, 125-μm-diameter, microthermocouple (Type T, Omega, Stamford, Connecticut) was positioned 1 mm above the sieve mesh and 3 mm from the center of the tube (at the tube wall), to monitor and record saline temperatures in close vicinity to the stone sample during laser ablation (Fig. 2). A digital data acquisition system (OM-USB-TC, Omega) connected to the microthermocouple and controlled by a laptop personal computer was used to record all temperature data. The peak temperature from each individual study (n = 12) of a given data set was recorded, and then the mean and standard deviation of all of these peak temperatures was calculated and are provided in Table 1. Great care was taken to prevent directly irradiating the thermocouple with laser energy from the fiber optic tip so as to avoid both potential damage to the thermocouple and erroneous temperature values from direct absorption of laser energy by the thermocouple.

3 Results
3.1 Laser and Operation Times
Mean laser and operation times during holmium:YAG and TFL lithotripsy experiments are summarized in Table 1. The laser was periodically turned off to allow re-positioning of the fiber and stone debris clearance for improved visibility during the procedure, which resulted in the reported differences between laser and operation times. The initial stone mass was similar for all data sets and measured 59 ± 4 mg for the holmium laser data set, and 55 ± 15, 60 ± 15, and 66 ± 10 mg for the TFL pulse times of 150, 300, and 500 Hz, respectively. Holmium laser times measured 167 ± 41 s. TFL times measured 111 ± 49, 39 ± 11, and 23 ± 4 s, for pulse rates of 150, 300, and 500 Hz, respectively. As the TFL pulse rate was increased from 150 to 500 Hz, laser times decreased since the laser pulses were more rapidly delivered to the stone. Operation times were also recorded. Holmium laser operation time measured 207 ± 50 s. TFL operation times measured 116 ± 54, 54 ± 22, and 60 ± 22 s for pulse rates of 150, 300, and 500 Hz.

Table 1 Total laser and operating times to fragment 4- to 5-mm diameter calcium oxalate stones into fragments smaller than 1.5 mm, and peak saline temperatures measured during experiments.

<table>
<thead>
<tr>
<th>Laser</th>
<th>Laser time (s)</th>
<th>Operation time (s)</th>
<th>Peak temperature (°C)*</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmium:YAG</td>
<td>167 ± 41</td>
<td>207 ± 50</td>
<td>24 ± 1</td>
<td>12</td>
</tr>
<tr>
<td>Thulium fiber laser</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 Hz</td>
<td>111 ± 49</td>
<td>116 ± 54</td>
<td>33 ± 3</td>
<td>12</td>
</tr>
<tr>
<td>300 Hz</td>
<td>39 ± 11</td>
<td>54 ± 22</td>
<td>33 ± 7</td>
<td>12</td>
</tr>
<tr>
<td>500 Hz</td>
<td>23 ± 4</td>
<td>60 ± 22</td>
<td>39 ± 6</td>
<td>12</td>
</tr>
</tbody>
</table>

*Baseline temperature was 22°C.

Both stone laser times and total operation times were significantly shorter for the TFL at all pulse rates (150, 300, and 500 Hz) than for the holmium laser (P < 0.05). However, there was no statistical difference between the 300 and 500-Hz TFL operation times (P = 0.37). These overall findings were due to a number of factors, including TFL operation at higher power densities, higher pulse rates, higher average powers, and reduced stone retropulsion, as described below.

The two lasers produced two different stone motion effects. The TFL with a lower pulse energy and higher pulse rate produced a vibrational effect, which led to the stone oscillating in the same relative position. The holmium laser exhibited a retro-pulsion effect, causing the stone to recoil within the confines of the ureter model, and making it more difficult to ablate the stone in an efficient manner, which was reflected by longer holmium laser and operation times provided in Table 1. It should be noted, however, that the presence of the sieve may have distorted to some degree the normal retropulsion movement typically encountered in the clinic.

3.2 Saline Temperatures
Mean peak saline temperatures (defined as average of n = 12 individual peak temperatures for each data set) during holmium:YAG and TFL lithotripsy experiments were calculated to be 24 ± 1°C for holmium, and 33 ± 3°C, 33 ± 7°C, and 39 ± 6°C for the TFL at pulse rates of 150, 300, and 500 Hz, respectively (Table 1). Temperatures during TFL lithotripsy were significantly higher than for the holmium laser (P < 0.05). The results also suggest that a decrease in the TFL pulse rate from 500 to 300 Hz also translated into a lower average power and lower saline temperatures (P = 0.01), and thus provides an additional safety margin for potential future clinical studies.

Temperature history graphs showing the worst case (highest peak temperature) during holmium and TFL lithotripsy experiments are provided in Fig. 3. The variation in temperatures in all of the graphs is due to a number of factors, including the laser parameters, experimental setup, and surgical technique. Specifically, variable laser pulse rates were used translating into different cooling rates in between delivery of individual laser pulses. The ureteroscope was handheld and the distance between the fiber optic tip and thermocouple location also varied constantly, affecting temperature readings as well.

The two laser systems produced different saline temperature profiles near the stone sample. During holmium laser lithotripsy, a small overall elevation in the saline temperature was observed, averaging only a few degrees Celsius by the end of the procedure. The highest temperature recorded for any of the stone samples was only about 26°C [Fig. 3(a)]. This minimal temperature rise may be explained by the low pulse rate (6 Hz) and low duty cycle (1:167) with sufficient time for saline cooling in between holmium laser pulses.

On the contrary, during TFL stone ablation there was a rapid and substantial increase in saline temperature, presumably due
to the higher duty cycles of 1:10, 1:5, and 1:3 for the TFL pulse rates of 150, 300, and 500-Hz operation, respectively, and correspondingly lower cooling times in between laser pulses. The highest temperature measured for any stone sample was 48°C [Figs. 3(c) and 3(d)]. However, such temperatures were maintained for a short time, typically less than 1 s [Fig. 3(d)] and less than 4-s total [Fig. 3(c)]. Such temperatures corresponded to the time when large stone debris or chips were obstructing the sieve, reducing irrigation rates, and temporarily resulting in a thermal buildup in the saline (Fig. 4). As expected, mean peak saline temperatures decreased as the TFL pulse rate was decreased from 500 to 300 Hz, due to lower average power and duty cycle, and longer cooling times in between laser pulses.

It is of interest that the TFL operation at 300-Hz led to a significant decrease in saline irrigation temperatures without decreasing overall operation times, in comparison with 500 Hz. It may be that although TFL operation at 500-Hz results in shorter laser irradiation times, the operating time is not reduced due to both greater stone movement and the need to more frequently pause during the procedure and momentarily turn the laser off for improved fiber positioning and visibility.

It should be emphasized that the saline temperatures recorded during TFL lithotripsy may be of potential concern during a clinical procedure, because a prolonged and excessive temperature rise, although not observed here, could possibly cause undesirable collateral thermal damage to surrounding soft tissues.

![Temperature versus time plots showing worst case (highest peak temperature) for holmium:YAG and thulium fiber laser (TFL) lithotripsy procedures.](https://www.spiedigitallibrary.org/journals/Journal-of-Biomedical-Optics)

**Fig. 3** Temperature versus time plots showing worst case (highest peak temperature) for holmium:YAG and thulium fiber laser (TFL) lithotripsy procedures. (a) Holmium laser, $T_p = 25.5^\circ$C; laser time = 288 s; total time = 320 s; (b) TFL at 150 Hz; $T_p = 38^\circ$C; laser time = 154 s; total time = 154 s; (c) TFL at 300 Hz; $T_p = 48^\circ$C; laser time = 43 s; total time = 47 s; (d) TFL at 500 Hz; $T_p = 48^\circ$C; laser time = 22 s; total time = 107 s. Note that the variation in temperatures measured was a function of not the only laser parameters used but also of the variable movement of the fiber tip and urinary stone sample with respect to the thermocouple position.

![Stone fragments after TFL lithotripsy.](https://www.spiedigitallibrary.org/journals/Journal-of-Biomedical-Optics)

**Fig. 4** (a) Stone fragments after TFL lithotripsy. Inset figure shows the original stone at the same scale. (b) Video frame showing multiple large stone chips temporarily obstructing the sieve and saline irrigation flow at the time point in which the absolute peak temperature of 48°C was measured by the microthermocouple during TFL lithotripsy at 500 Hz [Fig. 3(d)].
urinary tissues such as the ureter or kidney, if left unchecked. However, to put these specific results into proper perspective, it should be noted that even the highest temperatures reached (48°C) only briefly (<4 s), and are safe based on standard Arrhenius integral calculations for thermal damage to soft urological tissues using published values, as discussed in more detail below.

4 Discussion
During this study, both laser times and total operation times for stone fragmentation were significantly shorter for the experimental TFL operated at all pulse rates (150, 300, and 500 Hz) than for the conventional holmium laser (P < 0.05). This result was due to a number of factors, including TFL operation at a higher power density, higher pulse rates, and higher average powers. The observation of reduced stone retropulsion also played a role and was due in part to the use of lower TFL pulse energies and smaller optical fibers. It should be noted that the diode-pumped fiber laser technology such as the TFL is ideally suited to performing laser lithotripsy, where low pulse energies, high pulse rates, long pulse durations, and small optical fibers have been previously reported to be optimal for minimal stone retropulsion and more efficient stone ablation.

Other studies have recently been published exploring the influence of saline irrigation rates on ureter temperature profiles during holmium laser lithotripsy. For example, Molina et al., reported higher ureter wall temperatures of 37°C and 50°C for a ureteral stone model and an open ureter model, respectively, than was measured in our study. However, there were several significant differences between the two studies. For example, the holmium laser settings (1 J, 10 Hz, average power = 10 W) in Molina’s study were significantly higher than the settings in our study (0.6 J, 6 Hz, average power = 3.6 W), and the power density was also higher even after factoring in their larger 365-μm fiber versus our 270-μm fiber. Based on this difference alone, it is not surprising that their ureter temperatures during holmium laser lithotripsy were higher than those in our study. Our holmium laser settings were carefully chosen only after consultation with urologists about commonly used laser lithotripsy parameters. It should also be noted that Molina et al. used a saline pump to provide an extremely high constant saline flow rate of 8 ml/s or 480 ml/min. This flow rate is over 20 times higher than the flow rate in our study (22.7 ml/min) in which we used a normal gravitational flow alongside a 270-μm fiber through the ureteroscope working channel. Although saline pumps may provide a useful option for temporarily increasing saline irrigation rates, such an approach can also be dangerous in a clinical setting because it risks washing stone fragments back into the kidney and increases the probability of distending and rupturing the kidney. Finally, Molina et al. used a sheep ureter model compared with our artificial ureter model, and their ureter model was not placed in a saline bath, so peak temperatures would be expected to be higher than in our study.

A mathematical description in the form of an Arrhenius integral is the standard formulation for predicting laser-induced thermal damage to tissues. Thermal damage, quantified by Ω(t), can be evaluated using the Arrhenius integral: Ω(t) = ζ(t)0 exp[-Ea/(RT crit)]dt, where ζ (s⁻¹) is frequency factor; τ (s) is total heating time; Eα (J/mol) is the activation energy; R (8.32 J/K mol) is the universal gas constant; and T(t) is the absolute tissue temperature. Values of frequency factor (ζ) and activation energy (Eα), corresponding to amount of energy needed to start the transformation process, are derived from experimental analysis. The thermal damage parameter Ω(t) depends exponentially on temperature and linearly on heating time, and Ω(t) = 1 corresponds to 63% damage to the tissue. It is also useful to define the critical temperature for damage accumulation rate as, ΔΩ/Δt: ΔΩ/Δt = ζ exp[(-Eα/(RT crit))]. The critical temperature (T crit) is related to Ω(t), ζ (s⁻¹), and Eα. Below T crit, or the thermal damage threshold temperature, the damage accumulation rate is negligible. However, the damage rate increases exponentially when T crit is exceeded.

Unfortunately, there are currently no published Arrhenius integral parameters for ureter tissue. However, studies have been performed using other urinary tissues, such as kidney, and other elastic, tubular structures such as arteries, which may provide approximations for our case. The critical temperatures for kidney and arteries were reported to be 73.7°C and 79.15°C, respectively. The amount of time necessary to damage the ureter can be calculated using these critical temperatures along with their corresponding values for the frequency factor and activation energies provided in Refs. 13 and 14, assuming that Ω(t) = 1, and substituting the absolute peak temperatures observed in our TFL studies of T = 48°C. The resulting time periods at which the ureter has to be maintained at 48°C, for both kidney and artery approximations, are t = 18.5 and 424 h, respectively. Clearly, the peak temperatures achieved in our study are nowhere near the thermal damage temperatures for these times scales.

It may be possible to further increase the safety margin and reduce the probability of adverse heating effects during TFL lithotripsy by implementing a combination of safeguards, including (a) higher saline irrigation rates, (b) use of chilled saline, (c) delivery of laser pulses in short bursts of only a few seconds, and/or (d) further reduction in laser pulse rates. For example, syringe pumps are used in the clinic to temporarily provide increased pulsatile saline irrigation rates (e.g., 480 ml/min for Molina study) compared to normal gravitational flow of about 20 ml/min (with 270-μm fiber in working channel) from hanging a saline bag above the patient.

Future plans include further safety studies studying inadvertent TFL perforation of the ureter and kidney, as well as laser-induced thermal damage to ureteroscopic devices (e.g., stone baskets and guidewires). Incidents of ureter perforation and ureteroscope device damage from the holmium laser have been previously reported. It would, therefore, be informative to study how such TFL adverse incidents compare with the holmium laser. Several minor technical improvements to the TFL also need to be implemented prior to the translation of this technology into the clinic, including integration of a visible aiming beam into the laser system for alignment purposes and reduction of back-reflected light from the optical components.

5 Conclusions
The TFL was observed to fragment kidney stones more rapidly than the holmium laser in a comparative setting, due in part to the combination of the TFL’s high pulse rate, high average power, and reduced stone retropulsion. To avoid thermal buildup, TFL lithotripsy should be performed with pulse rates below 500 Hz and/or increased saline irrigation rates. Under these conditions, TFL lithotripsy may provide an alternative to conventional holmium:YAG laser lithotripsy.
References


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