Clinical Trial Evaluating the Efficiency of Holmium Laser Settings on Urinary Stones

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Project Summary

This is a prospective randomized study designed to assess the time required to fragment urinary stones to ≤ 2 mm, which is our current institutional practice, during surgical laser lithotripsy procedures. Specifically, we will compare the time to fragmentation required at low vs. high laser energy settings. Laser lithotripsy is a surgical procedure performed during stone surgeries. Literature and history have shown the holmium laser is a safe and effective method of treating a wide variety of urinary stones. Currently, at the University of Wisconsin, the urologist has the clinical authority to adjust the energy settings across a wide range when treating urinary stones. At our institution, a multitude of laser settings have been used regularly in clinical practice at the University of Wisconsin since 1995; an estimated 300 laser lithotripsy cases are performed annually in our department. Typically, we have evaluated surgical outcomes as part of routine quality improvement initiatives or as IRB-approved retrospective reviews. However, in this scenario, a randomized trial, which requires IRB approval, offers the ability to conduct a higher level study protocol and allows us to rigorously compare the time required for acceptable stone fragmentation using different laser energy settings. A randomized trial, unlike a retrospective review of our surgical procedures, will reduce bias sufficiently to allow us to be sure of our results.

Background & Significance

The incidence of urinary tract stone disease is increasing. According to the National Health and Nutrition Examination Survey, as of 2012, 10.6% of men and 7.1% of women in the United States are affected by renal stone disease (Scales et al 2012). Treatment of urolithiasis is commonly done using the holmium:YAG laser as this has been shown to be a safe and effective method of treating a wide variety of stones and is currently considered the standard of care (AUA Guideline Panel on the Surgical Management of Stones; Assimos et al J Urol 2016; Kronenberg & Traxer, World J Urol 2015). Holmium lasers allow the urologist to adjust the laser energy, measured in Joules (J). Urologists currently use a wide variety of laser settings during surgical procedures, (Bell et al, J Endo 2016). We have conducted in vitro testing of our holmium lasers showing that fragmentation efficiency is better when using higher energy settings (Bell et al – manuscript currently under review). Others have shown similar data in vitro, yet high quality, randomized, prospective clinical trials are lacking in this area (Hecht & Wolf, 2013; Sea et al, 2012). In this study, we are going to conduct a prospective, randomized clinical trial to determine if 0.8J energy setting result in faster fragmentation time clinically compared with 0.2J. Fragmentation time is significant as this may lead to shorter overall operative times, which can may result in decreased operative costs and complications (Bagrodia et al, J Urol 2009; Schuster et al, J Urol 2001).

Study Objectives

The primary objective of this study is to compare the time to acceptable stone fragmentation during clinical use of the holmium laser when using energy settings 0.2J vs 0.8J. Our hypothesis is that holmium laser energy settings 0.8J will require less time than lower energy settings 0.2J for fragmenting urinary stones. Our clinical practice is to treat urinary stones until the stone is reduced to fragments ≤ 2 mm in size. This is determined by using the laser fiber which is 273 microns to visually estimate the size of the resultant fragments as

described by Patel et al, J Endo 2014. We will standardize the effect of stone size by creating a ratio of stone size to treatment time. The frequency is set as 15Hz. Thus, the study contains two arms: 0.2J&15Hz, and 0.8J&15Hz. Patients will be randomized into the two groups by the ratio of 1:1.

Research Design and Methods

Design

This study will be a randomized trial comparing the 0.2J vs 0.8J energy settings of the holmium laser during surgical laser lithotripsy procedures. The primary objective is to calculate the fragmentation time (min). We will keep strict timing of laser time. The following information will be collected as well as secondary outcomes: (1) Total operative time; (2) Information regarding urinary stone including the size (pre-operative stone size in mm), location (renal or ureter), density, and number of stones treated. Size of fragments created will be assessed using the laser fiber size as a comparison (Patel et al, 2014). A total of 1 clinic visit (i.e., the stone surgery, approximately 5-6 hours, depending on the duration of the surgery) is needed for this study. Laser information (e.g., frequency, total energy used), postoperative complications, as well as demographic information and co-morbidities will be collected and recorded. Approximately 48 patients will be enrolled (see Data Analysis for sample size justification).

Patient Recruitment and Randomization

Patients who are to be scheduled laser lithotripsy treatment of urinary stones will be approached for study participation. They will be initially approached by a study team member who also works in the urology clinic (i.e. informed that there's a research study they may be eligible for, and asked if they want to learn more about it). All information about the study will be provided, and ample time will be made available for the participant to consider participation in the study. Eligibility screening (by reviewing patients' medical record that is relevant for inclusion/exclusion criteria) will occur after consent form is signed. Patients who meet the inclusion criteria in the study will be randomized (ratio 1:1) on the day of surgery to be treated with either 0.2J or 0.8J laser during lithotripsy.

Study Procedure

1. A study team member who is affiliated with the patient's clinical care (e.g., the surgeon) will initially approach the patients who are scheduled laser lithotripsy treatment of urinary stones. (i.e., informed that there's a research study they may be eligible for, and asked if they want to learn more about it).
2. If the patient is interested in the study, a member of the research team will approach him/her for enrollment.
3. Once the consent form is obtained, patients' medical background will be reviewed for inclusion/exclusion criteria. Patients who meet the inclusion criteria will be included in the study; patients who do not meet the inclusion criteria will be excluded.
4. Patients will be randomized to either 0.2J&15Hz or 0.8J&15Hz (randomization ratio 1:1) group.

5. Patients will undergo stone surgeries with the laser setting that they are randomized to. The patient's stone(s) will be treated in accordance to our routine clinical practice of fragmenting stone into small pieces (≤ 2mm). The faculty surgeon (i.e., Dr. Nakada) will perform all surgeries.
6. Fragmentation time as well as other information (see study design for the detail information) is collected.
7. After surgery, the patients will then continue on our normal postoperative pathway. Postoperative complications will be collected.

Inclusion Criteria

- Patients at least 18 years of age
- Patients with urinary stones who require endoscopic treatment

Exclusion Criteria

- Patients < 18 years of age
- Pregnant patients
- Pre-menopausal females who have not been on approved birth control for at least 1 month pre-operatively
- Patients with stones known to be refractory to treatment with the holmium laser

Intervention:

The only interventions imposed on subjects as a result of this study are (1.) pre-procedural randomization to laser lithotripsy with either 0.2J or 0.8J energy setting, and (2.) the use of patient information in describing our results. All the other activities are part of our routine clinical practice. Participation in the study will not alter the patients' preoperative, or postoperative care. During surgery, patients' stones will be treated in accordance with our routine clinical practice of fragmenting stones into small pieces (<2 mm). All patients enrolled will undergo routine post-operative follow up including clinic appointments and imaging evaluation. Any complications will be recorded, reported, and treated appropriately.

Device Description

Holmium lasers will be used for this study, which are currently the standard of care for treating urinary stones through an endoscope. The energy settings will range from 0.2J to 1.5J, frequency settings of 5Hz to 80Hz. Laser settings are routinely changed during surgery. All of these settings have been used in patients since early 1990s and are all considered clinically relevant and safe settings..

In the current study, the laser settings are 0.2J&15Hz and 0.8J&15Hz. Although the two exact settings are somewhat arbitrary, all these settings mentioned above have been approved optimal for holmium:YAG lithotripsy without significant complications (e.g., Ilker et al International Urology and Nephrology 2005; Razzaghi et al Endourology and Stone Disease 2013; Waterson et al the Journal of Urology 2002). Both laser settings are routinely used in our clinical practice. The randomization to either group will not influence anesthesia time.

Safety Monitoring Plan

The standard treatment for endoscopic treatment of urinary stones is the use of the holmium laser, thus the patients will be treated with the same modality, as they otherwise would have if they were not involved in a research study. This modality has been shown to be safe and effective and has been used at the University of Wisconsin since 1995. The holmium laser devices are approved for the treatment of urinary stones in humans using a variety of settings (Denstedt, 1995; Johnson, et al, 1992; Sayer et al, 1993; Webb et al, 1993). In patients who are treated with energy settings 0.8J, there is a theoretical small risk of clinically significant injury to the urothelium. The assignment to the low energy setting laser treatment may be associated with a longer period of time to fragment stones, extending surgery duration and anesthesia time. This could be associated with an increase in the likelihood of the standard risks associated with anesthesia. Thus, the faculty surgeon (i.e., Dr. Nakada) will perform all surgeries. The Endourology Fellow will assist the surgeon in the stone surgery. If significant injury or inefficient fragmentation of the stone occurs, the surgeon will have the discretion to alter the settings for patient safety reasons. The data will be analyzed as an intention-to-treat analysis.

Participation in the study will not alter the patients' preoperative, or postoperative care. All patients enrolled undergo follow up the routine post-operative procedures for complications. Complications will be recorded and treated. Patients may choose to withdraw from study at any time without repercussions to subsequent care.

Regular inquiries of study flow, pertaining to patient recruitment, randomization, and adverse events will be scheduled to occur after the first week and subsequently every two weeks. Any adverse events will be monitored as per standard protocol in clinical use. A comparison of adverse events between groups (e.g., to determine whether those assigned to the 0.8J energy group are experiencing more frequent or serious adverse effects) will be included. No significant adverse events are anticipated in the current laser settings, as they are routinely used urology practice. Any adverse events or unanticipated problems will be reported to the PI and IRB, and treated accordingly. In addition, members of the study team will be performing these procedures and will monitor the patient during treatment for any signs of complications.

Confidentiality

All electronic data will be stored on a HIPAA compliant department server which is maintained on password and firewall-protected computers in locked offices of the Department of Urology, located in a security-protected building (MFCB). Data to be analyzed after extraction. A single copy of the master code sheet linking medical records numbers and the coded data sets will be created and stored on a password and firewall-protected computer in a locked office in a security-protected building (MFCB). Only key personnel listed on this study will have access to this information. All analysis files will be devoid of patient identifiers.

Data Analysis

The data collected will be analyzed as an intention-to-treat analysis. All patients enrolled will undergo routine post-operative follow up including clinic appointments and imaging evaluation. The primary outcome is the treatment time (i.e., fragmentation of stones to <2 mm)

required for each study arm. Statistical analyses will include T-test and, if appropriate, Chi-square tests (e.g., for categorical data). Patient demographics and stone characteristics will be summarized as appropriate as continuous variables (mean and standard deviation) or categorical variables (frequency, percentage).

We plan to enroll 48 patients for this study. A two-tailed T-Test will be used for data analysis.

In the intro data, the frequency for 0.2J were 40 (0.2J&40Hz, N=4, Mean=30, Standard Deviation= 8.728) and 70 (0.2J&70Hz, N=4, Mean=24.07, Standard Deviation= 1.386), and the frequency for 0.8J was 8 (0.8J&8Hz, N=8, Mean=25.1113, Standard Deviation= 5.1509). Based on this data, we assume the Mean (0.2J&15Hz)=40mins, and Mean (0.8J&15Hz)=24mins with a standard deviation of 6. Thus, the hypothesized effect size is 2.667.

However, the in vitro study is an ideal setting for stone fragmentation. It also involves significantly more heterogeneity (larger standard deviation) than a standardized phantom, this will be mitigated by stone characteristics (e.g., stone volume, composition, location). Thus, we assume that *in vivo* heterogeneity is a factor of two times larger than that observed in the *in vitro study.* Thus, the hypothesized Cohen's d=1.33.

We also plan to stratify results by other factors, such as stone location (i.e., renal or ureteral), patients' characteristics (e.g., BMI, gender, age), and other comorbidities. To ensure the statistical power, we decide to set the p value as 0.01. Thus, approximately 32 patients in total are needed (16 subjects per arm) for a two-tailed T test with an 80% power and an alpha of 0.01. We also decide to increase the sample size by 50%. Thus, approximately 48 patients are needed for the current study. This number allows for the possibility that the randomization scheme is intra-operatively abandoned for some reason (e.g., equipment failure), that patients who signed the consent form but do not meet the inclusion criteria will withdraw, that the planned procedure was unable to be completed for some reason, as determined by the surgeon in charge of the case, and/or that the patient – after his/her procedure – wishes to withdraw from the study and exclude his/her information from our analysis. Besides fragmentation time, we will also analyze the postoperative complications to determine side effects for both power settings.

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