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Randomized Clinical Trial Evaluating the Efficiency and Safety of Holmium Laser with Moses Technology versus SuperPulsed Laser System with Thulium Laser on Renal and Ureteral Stones

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PROTOCOL TITLE:

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	6/14/2021	Initial IRB review modification requests	Yes
2	7/22/2021	Change of protocol	No
3	8/30/2021	Change of protocol	No

Project Summary

This is a prospective randomized controlled trial designed to assess the efficiency of Lumenis® Pulse™ P120H holmium laser system with the Moses technology (holmium laser with Moses) versus the Soltive™ SuperPulsed Laser System with the thulium fiber laser technology (thulium laser), in fragmentation of upper tract urinary stones during ureteroscopy with laser lithotripsy. Specifically, we will compare procedural time, intra-operative parameters and stone free rates. Laser lithotripsy is a surgical procedure performed during stone surgeries. Both lasers are FDA approved and clinically used in the United States. Currently, at University of Wisconsin, we are using the holmium laser with Moses during ureteroscopies and we will soon have the thulium laser for clinical use as well. At our institution, we perform approximately 200 outpatient ureteroscopies with laser lithotripsy annually. 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 requiring IRB approval, we have the ability to conduct a higher-level study protocol and rigorously compare the time required for acceptable stone fragmentation using the two different lasers. A randomized trial, unlike a retrospective review of our surgical procedures, will reduce bias sufficiently to allow us to be sure of our results.

Number of Study Sites

UW, Department of Urology only

Background and 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.[i] This has led to an increased demand on Urologists for efficient and safe surgical treatment of stone disease. Over the past two decades, ureteroscopy with laser lithotripsy has become the treatment of choice for most ureteral and renal stones globally.[ii] The holmium laser is considered the gold standard for laser lithotripsy.[iii] Holmium laser lithotripsy with Moses and the thulium laser are new technologies meant to improve the efficiency of laser lithotripsy. Both are FDA approved treatment modalities for stone disease. Two in vitro studies have compared Moses versus thulium and shown that thulium has higher ablative volumes then the holmium laser with Moses, but no clinical trials have compared the two treatment modalities.[iv,v] In this study, we are going to conduct a prospective, randomized clinical trial to determine whether there is a difference in procedural time, intraoperative parameters or stone free rate between the Holmium laser with Moses and the thulium laser. This is significant as this may lead to shorter overall operative times, which may result in decreased operative costs and complications. [vi,vii]

Study Objectives

The primary objective of this study is to compare the procedural time to acceptable stone fragmentation during clinical use of the holmium laser with Moses and the thulium laser. Our hypothesis is that the thulium laser will have decreased procedural time compared to the holmium laser with Moses. Secondary outcomes will include intra-operative parameters and post-operative parameters. 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 (A 200 micron fiber will be used with both groups), to visually estimate the size of the resultant fragments.[viii]

The secondary objective is to compare the primary and secondary outcomes when stratified by stone size. This will allow us to explore the efficiency between Moses and thulium laser on treating large vs. small stones. Previous literature suggested that stone size was associated with operative time.[ix] Patients will be separated based on the size of their stones: 3-10 mm or 11-20 mm and then randomized to holmium laser with Moses or thulium laser. Patients will be randomized into the groups by a ratio of 1:1.

Research Design and Methods

This study will be a randomized trial comparing ureteroscopy with laser lithotripsy with the Lumenis® Pulse™ P120H holmium laser system with the Moses technology (holmium laser with moses) versus the Soltive™ SuperPulsed Laser System with the thulium fiber laser technology (thulium laser). The primary objective is to compare the procedural time (minutes). We will keep strict timing from the minute the ureteroscope is inserted into the patient to the time the ureteroscope has been removed. The following information will be collected as secondary outcomes: (1) stone free rate; (2) total operative time (minutes); (3) fragmentation/dusting time (minutes, total time to fragment the stone, including the laser was in use and time of pedal pauses); (4) lasing time (minutes, time the laser was in use, not including pedal pauses); (5) total energy used (kilojoules, kJ); (6) laser efficiency (mm per minute); (7) number of times the laser pedals are pressed (left, right, and total pedal presses); (8) stone analysis; (9) complications; (10) quality of life survey (WISQOL short form) both pre-operatively and post-operatively and (11) physician evaluation of the laser. Physicians will complete a one page survey at the end of the case evaluating the laser (survey included as attachment). A total of 3 clinic visits (i.e., pre-operative visit, the stone surgery, and one post-operative visit) will be needed for this study. Stone parameters (i.e. size, location, Hounsfield units, presence of hydronephrosis, stone volume), demographic information, co-morbidities, and post-operative parameters will be collected from the medical record.

Number of Participants

Approximately 164 patients will be enrolled (see Data Analysis for sample size justification).

Inclusion Criteria

1. Patients at least 18 years of age, and less than 89 years old.
2. Patients with renal or ureteral urinary stones who require endoscopic treatment in the outpatient operating room
3. Patients' stone size in a single renal unit of 3-10 mm and 11-20 mm. Stone size is defined as the largest diameter of a single stone on pre-operative CT. Patients with multiple stones will be included as long as their largest stone size falls within the above parameters.

Exclusion Criteria

1. Patients under 18 years of age and over 89 years old.
2. Pregnant patients
3. Patients with transplant kidneys
4. Patients with irreversible coagulopathy
5. Patients with known ureteral stricture disease
6. Patient who do not have a pre-operative CT.
7. Non-English speaking, vulnerable patients such as lacking of decision-making capability, prisoner, adult unable to consent, will not be enrolled.

Recruitment methods

Patients who are to be scheduled for laser lithotripsy treatment of urinary stones as outpatients will be approached for study participation. During patients' pre-operative clinic visit, eligibility screening (by reviewing patients' medical record that is relevant for inclusion/exclusion criteria) will occur before recruitment. If patients meet the inclusion criteria, they will be initially approached by a study team member who also works in the urology clinic (i.e., the surgeon informs the patient that there's a research study they may be eligible for, and asked if they want to learn more about it).

No other recruitment materials will be used in this study. Holmium laser with Moses or thulium laser to treat stones is our routine care. Patients have been informed about the laser lithotripsy treatment before they schedule their surgery. We will only recruit patients from the outpatient OR, so this will not include patients who come in emergently through the Emergency Department.

No compensation will be provided to participants.

Consent Process

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 for 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).

If the patient is interested in the study, a member of the research team will approach him/her for enrollment. Consent process will be conducted face to face. Participants will be provided a written consent form in person. No waiting time is expected between informing the prospective participant and obtaining the consent.

Consent will take place during patients' pre-operative clinic visit. If patients are interested and there is not enough time to consent the patient in urology clinic, study information will be sent home with the patient and the patient will then be consented before their surgery in a private room (pre-operative room). Pre-operative room provides 1-1 1/2 hours of time. This should be ample time to conduct the consent process before surgery anesthesia.

All information about the study will be provided, and ample time will be made available for the participants to consider participation in the study.

Patient Randomization

Patients will be randomized (ratio 1:1) at the time of enrollment to be treated with either the holmium laser with Moses or the thulium laser. We will use Permuted Block Randomization (stratified by stone size 3 - 10 mm or 11-20 mm) (block size 4).

Study Procedures

1. The study team members review patients' medical record during patients' pre-operative clinic visit to see whether patients meet inclusion/exclusion criteria.
2. If patients meet the inclusion criteria, 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 for 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).
3. If the patient is interested in the study, a member of the research team will approach him/her for enrollment.
4. Patients will be asked to fill out a WISQOL short form at their pre-operative visit. This is standard of care for all stone patients in clinic.

5. Patients' total stone size (pre-operative CT) will be calculated and divided into two groups. Those with stones 3-10 mm and those with stones 11-20 mm. They will then be randomized to either the holmium laser with Moses or the thulium laser (randomization ratio 1:1) group.
6. Patients will undergo stone surgeries with the laser that they are randomized to. A 200 micron fiber will be used with both machines. The patient's stone(s) will be treated in accordance with our routine clinical practice of fragmenting stone into small pieces (≤ 2mm). One stone fragment will be collected for stone analysis if the patient does not already have a stone analysis on file (this is also standard of care). The faculty surgeons will perform all surgeries. We are unable to blind the surgeon to the laser used as the laser fibers and laser machines appear and sound different.
7. Procedural time as well as other information (see study design for the detail information) is collected.
8. After surgery, the patients will all have at least an abdominal x-ray within 1 month of surgery, if a CT scan has not already been completed(this is the standard of care). They will also be asked to fill out a WISQOL short form at their one-month follow up appointment. Otherwise, they will continue on our normal postoperative pathway. Postoperative complications will be collected.

Comparison of usual care and study procedures

Compared with our routine care, the only interventions imposed on subjects as a result of this study are (1) pre-procedural randomization to laser lithotripsy with either holmium laser with Moses or thulium laser, and (2) the use of patient & surgery information collected in describing our results. All the other activities are part of our routine clinical practice. Participation in the study will require a pre-operative CT abdomen without contrast, which is standard of care, as well as at least an abdominal x-ray post operatively which is also standard of care. Four surgeon will perform the ureteroscopy (i.e., Nakada, Best, Hedican, Gralnek, and Knoedler). During surgery, patients' stones will be treated in accordance with our routine clinical practice of fragmenting stones into small pieces (<2 mm). Surgeons will use a 200 micron fiber for both the holmium laser with Moses and the thulium laser, but they will have the discretion to switch to a different fiber (ex. 150 micron thulium fiber) if they feel it is necessary during the case (if the surgeon changes the fiber during the surgery, the data will be analyzed separately). A stone fragment will be collected for stone analysis if the patient does not have one on file. This is our standard of care suggested by AUA guideline.[x] All patients enrolled will undergo routine post-operative follow up including clinic appointments and imaging evaluation (with at least an abdominal x-ray). An abdominal x-ray is used for follow up of nephrolithiasis and provides significantly less radiation, and it is our routine care. However, if the patient already has a CT completed by the follow-up visit, an x-ray is not needed. WISQOL short form will be administered during the pre-operative appointment and at the post-operative appointment, which is standard practice in our clinic.

Withdrawal of participants

Patients can withdraw anytime. Once they decide to withdraw, they will continue their standard clinical care with us. We will continue to collect patients' information from patients' medical records for their routine medical care.

Study Intervention

Holmium laser with Moses and thulium lasers will be used for this study. Both are FDA approved lasers for the treatment of urinary calculi through an endoscope. The holmium laser with Moses emits two separate laser pulses with a short time interval between them. The first pulse divides the water between the laser fiber tip and the stone and the second pulse hits the stone unobstructed.[xi] The goal is to increase stone ablative volume and decrease retropulsion of the stone. The thulium laser has a different wavelength then the holmium laser with Moses and thus has slightly different energy properties. It has also been shown to increase ablative volume and decrease retropulsion without any safety concerns.[xii] The holmium laser with moses is currently the most common laser used at our institution for treatment of urinary stones. The thulium laser has been used at our institution on a trial basis previously and will be available soon for use on a daily basis for surgical cases at our institution. There is no learning curve associated with the thulium laser. The two lasers have similar specifications; the two fibers are the same size and will interact with the instruments (ureteroscopes) similarly.

Study Timelines

For each patient, the study duration is from consent to the one-month post-operative clinic visit. Patients will be on study for approximately 6-8 weeks.

Risks and Potential Benefits

Treatment with the holmium laser with Moses and thulium laser can be associated with the common risks of hematuria, stent pain, passing fragments, UTI, dysuria. The rare risks include perforation of the urinary tract, bleeding, and stricture of the ureters. However, the surgeon who will perform the surgery will not exceed safe levels. All procedures performed by surgeons who are board-certified. If significant injury or inefficient fragmentation of the stone occurs, the surgeon will have the discretion to transition to a different laser for patient safety reasons. 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.

There is a risk that your information could become known to someone not involved in this study, which might make you uncomfortable.

There is no direct benefit. Potentially, more efficient laser may be identified which may result in faster procedural time and lower complication rates.

Safety Monitoring Plan

All procedures performed by surgeons who are board-certified. If significant injury or inefficient fragmentation of the stone occurs, the surgeon will have the discretion to transition to a different laser for patient safety reasons (The data 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. Any complications will be recorded, reported, and treated appropriately.

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. The lead researcher, Dr. Nakada, will be responsible for the inquiries. 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 thulium laser group are experiencing more frequent or serious adverse effects) will be included. No significant adverse events are anticipated for the lasers, as they are routinely used in 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.

Date Management and 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. Data to be analyzed after extraction. All paper records (such as WISQOL) will be saved in a locked office/cabinets of IRB approved study staff. Only key personnel listed on this study will have access to this information. All data analysis files will be devoid of direct patient identifiers. Direct identifiers will be destroyed at study closure or at the time of publication. De-identified data will be stored for potential future studies that have proper approval.

Since we have 5 surgeons participating in this study, we will use university-based cloud service (such as OneDrive) to temporarily save the enrollment log. Study team member will use their Net ID to access the enrollment log. The enrollment log is completely deidentified. Only participant ID (such as 101, 102) and the laser each participant is randomized to are saved in the enrollment log. Once we complete data collection, we will permanently delete it from the cloud.

Share of results

Some of the information collected for this study will go in the patient's medical record. This includes the results of the one-month post-operative image, stone analysis, stone surgery, and all clinic visits information as these are being conducted as standard of care. All other information from research specific procedures will NOT go in the patient's medical records.

We only publish aggregated results. No individual results will be shared. We will not share the data with outside institutions.

Economic burden to participants

This study does not place financial burden to patients. The study interventions are our routine clinical practice to treat stones. It will be same as they are not involved in this study.

The cost of the two laser treatments are equivalent.

Data Analysis

The data collected will be analyzed as an intention-to-treat analysis. Statistical analyses will include T-test and, if appropriate, Chi-square tests (e.g., for categorical data), and two-way MANOVA. Patient demographics and stone characteristics will be summarized as appropriate as continuous variables (mean and standard deviation) or categorical variables (frequency, percentage). To compare the two groups, continuous variables such as procedural time, total OR time, WISQOL etc., will be analyzed using T test and two-way MANCOVA (stratified by stone size 3 - 10 mm or 11-20 mm). The surgeon will be controlled as a covariate. Categorical variables such as stone free rate will be analyzed using chi-square.

We plan to enroll 164 patients in this study. Patients will be stratified into two groups according to their stone size (3-10 mm or 11-20 mm) and then randomized to either holmium laser with Moses or thulium laser. The stone size is defined as the largest stone size (largest diameter on pre-operative CT), if patients have multiple stones. Previous literature suggested stone size is associated with operative time.[ix] A significance level of 0.05 will be used with a two-sided two-sample equal-variance t-test. Group sample sizes of 33 and 33 achieve 80% power to detect a significant difference between the means when the mean difference is 4.6 minutes with a standard deviation of 6.5 minutes. We also decide to increase the sample size by 25% (41 patients per group). This will allow for the possibility that the randomization scheme is intra-operatively abandoned for some reason (e.g., equipment failure), 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.

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