Superpulsed Thulium Fiber Laser VS. Pulse Modulated High Power Holmium:YAG Laser For Retrograde Intrarenal Surgery

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Protocol Number*: 22-01521

Principal Investigator*: Mantu Gupta MD.

Sponsor: Mount Sinai, Department of Urology

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1.1 SYNOPSIS

Title: SUPERPULSED THULIUM FIBER LASER VS. PULSE MODULATED HIGH POWER HOLMIUM: YAG LASER FOR RETROGRADE INTRARENAL SURGERY

Grant Number: *N/A*

Study Description: This is a randomized prospective study comparing the stone free rate and operative efficiency of two leading contemporary laser systems used during retrograde intrarenal surgery for kidney stone disease. We will compare the following two systems:

1. A superpulsed thulium fiber laser (thulium)
2. A pulse modulated high power holmium laser (Holmium)

Objectives*:

Aim: To determine which laser system has superior outcomes as measured by post-operative stone-free status and intraoperative efficiency metrics

Research Question: During retrograde intrarenal surgery for kidney stone disease, which contemporary laser system (thulium vs. holmium) has a superior stone free rate?

Null hypothesis: During retrograde intrarenal surgery for kidney stone disease, there is no difference in stone free rates between the two laser systems.

Alternative Hypothesis: During retrograde intrarenal surgery for kidney stone disease, the thulium laser has a superior stone free rate.

Endpoints*:

Primary Endpoint:

- Stone-free status as determined by a post-operative CT scan.

Secondary Endpoints:

The secondary endpoints to be collected will pertain to efficiency metrics as produced by the laser systems:

- Fragmentation speed = stone volume/lasing time (mm3/sec)
- Energy Utilization = Laser energy/volume of stone (J/mm3)
- Lasing Activity: Lasing time/lithotripsy operative time (%)
- Operative time (minutes)
- Lasing time (seconds)
- Lithotripsy operating time (seconds)
- Treatment time (seconds)

Study Population:	We anticipate a sample size of 82 subjects enrolled in this study. Adult patients 18-years of age and older with non-obstructing kidney stones undergoing planned retrograde intrarenal surgery with laser lithotripsy.
Description of Sites/Facilities Enrolling Participants:	Dr. Gupta currently operates twice a week at Mount Sinai West (formerly Mount Sinai Roosevelt Hospital), located at 1000 10th Avenue, NY, NY 10019. In addition, he sees patients in the clinic at the following sites: Department of Urology Faculty Practice at 425 W. 59th Street, Suite 4F; Midtown Urology FPA at 625 Madison Avenue. Patient enrollment will occur at these clinical sites, while data collection will occur in the operating room at Mount Sinai West. Data analysis will occur at a site within the Mount Sinai Health System.
Description of Study Intervention/Experimental Manipulation:	The study intervention includes comparing two standard of care laser devices for laser lithotripsy of kidney stones. The laser device allocated to each study subject will be allocated by blinded randomization.
Study Duration*:	*24 months*
Participant Duration:	*3 months*

1.2 SCHEMA

Pre-Screening
Day -30 to Day 1

Pre-screen potential participants by inclusion and exclusion criteria during office consultation schedule.

Visit 1

Conduct informed consent process in pre-operative area day of surgery

Randomize
(n=82)

Ho: YAG	Thulium
N = 41	N = 41

Visit 2
Week 8
± 2 Weeks

Follow-up visit

Final Assessments
Stone free rates evaluated
by CT scans

Effective Date: 10/1/2024
End Date:9/30/2025

1.3 SCHEDULE OF ACTIVITIES

	Screening	Visit 1 Day 1 (Surgery)	Visit 2 Week 8 ± 2	Unscheduled Visit
EMR Review Eligibility	X			
Informed Consent		X		
Demographics	X			
Clinical history	X			
Height & Weight	X			
Outcome Evaluation				
Stone Free Rate			X	
Efficiency Metrics		X		
Randomization		X		
Control & Experimental Interventions		X	X	
Adverse Events Reporting		X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE/BACKGROUND

Kidney stone disease is one of the most common and painful conditions encountered in urologic practice. Retrograde intrarenal surgery with laser lithotripsy is the most commonly used standard of care treatment option for kidney stones and has been utilized for several decades. Advances in laser technology have progressively improved the efficacy and efficiency of the procedure. Currently, two laser systems are widely considered to be the most efficacious for this procedure: the superpulsed thulium fiber laser system and the pulse modulated high power holmium:YAG laser system. We routinely utilize either of these laser types when performing retrograde intrarenal surgery with laser lithotripsy for renal stones. However, to date, there have been no high-quality head-to-head randomized controlled trials comparing these two laser types to one another.

The closest such study compared the superpulsed thulium fiber laser system to an antiquated holmium: YAG laser system without pulse modulation and high-power output capabilities. The former resulted in a superior stone free rate (86% vs. 49%). However, the relative efficacy of the superpulsed thulium fiber laser compared to a contemporary pulse modulated high power Holmium:YAG laser remains largely unknown. To this end, the present study is a randomized prospective study comparing the stone-free

rate and operative efficiency of these two leading contemporary laser systems used during retrograde intrarenal surgery for kidney stone disease.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

With the exception of data-safety risk, participation in this study offers no additional risk compared to non-participation. Excluding data safety risk, the risks of participation are inherent to the standard of care procedure that the patient has consented to regardless of their participation in the study (retrograde intrarenal surgery with laser lithotripsy). These risks include bleeding, infection, damage to surrounding structures, and postoperative pain, which are inherent in all surgical procedures.

2.2.2 KNOWN POTENTIAL BENEFITS

There are no potential benefits to participants.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This study involves randomization of patients to one of two available laser systems that are used as standard of care for the treatment of kidney stones. In our practice, both laser systems are readily available and routinely used as a matter of surgeon preference and can be used interchangeably. This study poses no additional risks (outside of data-safety risk) to patients undergoing retrograde intrarenal surgery, which would have been recommended regardless of whether the patient was a study participant. Risks related to retrograde intrarenal surgery include infection, bleeding, and pain. These potential risks commonly exist with surgery but are rarely expected with this type of surgical procedure

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
To determine which laser system (if any) offers superior efficacy.	Stone free status as determined by 2-month postoperative CT scan	Stone free status on 2 month follow up CT scan is the most accurate evaluation for complete resolution of a patient's kidney stone burden	*N/A*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Secondary			
To determine which laser system (if any) offers superior efficiency.	Fragmentation speed, lasing activity, and energy utilization	These intraoperative laser metrics allow for the evaluation of intraoperative laser efficiency	*N/A*

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a randomized prospective study comparing the stone free rate and operative efficiency of two leading contemporary laser systems used during retrograde intrarenal surgery for kidney stone disease.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Randomization allows for elimination of potential bias. Because both laser systems are used routinely in the OR as a matter of surgeon preference, any source of bias will be prevented by using a randomized study design.

4.3 JUSTIFICATION FOR INTERVENTION

Both laser interventions are used as standard of care but a head-to-head comparison of the stone free rates has not been studied in a prospective randomized study. Study participation requires no additional visits or excessive effort placed upon the study participants as standard of care intervention and follow will be the same regardless of study participation or not.

4.4 END-OF-STUDY DEFINITION

The study will end when all patients have been enrolled and data has been analyzed.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

- Undergoing single stage unilateral RIRS for total stone burden volume >5mm to < 20 mm
- Must have preop CT scan to measure HU and measurements

5.2 EXCLUSION CRITERIA

- Anatomic variations: horseshoe kidney, pelvic kidney, ptotic kidney, urinary diversion or ureteral stricture
- Ureteral stent
- Uric acid component >50% on stone analysis
- Prior ureteroscopy within 6 weeks of current surgery
- Irreversible coagulopathy
- Urothelial tumor(s), direct extraction of the stone(s) without needing laser lithotripsy, and failure to reach the stone in the upper urinary tract with the ureteroscope.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be recruited from Dr. Gupta's practice. Dr. Mantu Gupta is a world-renown endourologist specializing in the treatment of kidney stone disease. The other members of the research team are currently working under the auspices of Dr. Gupta and are Mount Sinai clinical and research employees. The clinical staff is involved in this research study have direct access to Dr. Gupta's patient population and are involved in developing patients' treatment plans and managing patient care on a regular basis. The research staff is well trained to design and carry out the administrative and research aspects of this study. They are primarily responsible for educating and consenting patients for the study, and collecting and analyzing data, while ensuring that human research subjects are protected throughout their participation in this study.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

For subjects receiving URS, randomization will occur preoperatively. These subjects will be randomized to undergo lithotripsy with either Ho:YAG or TFL lasers.

All subjects will undergo surgical interventions that abide by broadly accepted guidelines and standards of care, allowing for slight variations in technique as seen necessary by the attending surgeon Dr. Gupta.

The type of laser that is chosen in SOC is based on hospital availability. That is, most hospitals only have one laser type to choose from (and that laser type is generally contingent on the biomedical contracts the

hospital holds with the various laser manufacturers). We are uniquely situated at Mount Sinai West in that we have multiple laser systems to choose from. Multiple surgeons share the lasers, and typically Dr. Gupta will use whichever laser is already in the room or readily available. Approximately 50% of ureteroscopies were performed with each laser, +/- 10%.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Dr. Mantu Gupta, professor of urology at Mount Sinai West Hospital will be performing the procedures. Dr. Gupta is a world-renowned expert in these operative techniques.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Patients will be randomized to receive either Thulium or Holmium laser lithotripsy. Patients will be blinded as they will be anesthetized during the operation. Blinding of the operators would not be possible owing to the differences in laser modalities.

We will utilize random.org which is a validated tool that utilizes atmospheric noise to generate random numbers. Each enrolled patient will be given a subject ID and these study IDs will be entered as string of integers to random.org and randomized prior to the initiation of the study. This process will determine group assignments. This will ensure both true randomization and equal allocation.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

No discontinuation will take place as the surgical procedures being performed are part of subjects' standard clinical care.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patients will be considered enrolled in the study once consent has been signed. Participants may discontinue or withdraw from the study for any reason and at any point in time through the conclusion of the study. If a participant desires withdrawal after some or all of their urine samples have been collected or analyzed, their urine samples will be discarded in a biohazard-safe and anonymous fashion.

7.3 LOST TO FOLLOW-UP

All study visits are performed according to the standard of care, and very little failure to follow up is expected.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1.1 DEFINITION OF ADVERSE EVENTS

Any untoward medical occurrence, unintended sign, symptom, illness or disease temporally associated with the study protocol regardless of the suspected cause.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An Adverse Event that is considered "serious" if it meets at minimum one of the three Seriousness reporting criterions below:

1. Led to death,
2. Led to a serious injury which:
    a. Resulted in a life-threatening illness or injury, or
    b. Resulted in a permanent impairment of a body structure or a body function, or
    c. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

8.1.2.1 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All AEs will be assessed for relationship to the study protocol based on the following definitions:

Not Related: There is no clear evidence that the AE has a relationship to the study protocol and can be attributed to an underlying or concurrent illness/clinical condition or an effect of another device, drug or treatment.

Related: There is a clear causal relationship of the AE to the marketed device or procedure beyond reasonable doubt.

8.1.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All enrolled subjects will be monitored for adverse events by review of the medical record on a monthly basis by Dr. Gupta. Subjects will have routine follow up scheduled postoperatively at which time in-person visit will be performed and assessment of adverse events may be performed.

8.1.4 ADVERSE EVENT REPORTING

Adverse events must be reported to the IRB as soon as possible and no later than **2 working days** after the PI first becomes aware of the event. The PI or designee must record all AE information that can be gathered within the reporting timeframe and enter it onto the AE eCRF.
Relevant follow-up information should be submitted to the IRB as soon as it becomes available and/or upon request.

8.1.5 SERIOUS ADVERSE EVENT REPORTING

See section 7.1.4

8.1.6 REPORTING EVENTS TO PARTICIPANTS

All SAE's or AE's will be reported to affected participants by the principal investigator directly.

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

A sample size of 82 patients will be accrued locally. We are enrolling 82 patients to allow for any potential exclusions due to failure to follow up. Ulvik et.al found a stone free rate of 66% and 33% respectively for the thulium fiber laser and holmium laser respectively. Our statistical analysis is to evaluate the superiority of the two laser modalities regarding stone free rate. With an allocation ratio of 1:1, 80% power, alpha of 5%, 66% stone free success of the thulium fiber laser, and 33% stone free success of the holmium laser, our sample size is 33 in each study arm for a total of 66 patients. Based on these calculations and factoring in a 20% dropout rate, we seek to enroll 82 total patients.

9.2 POPULATIONS FOR ANALYSES

All enrolled subjects will be included for analyses.

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

Baseline patient and operative characteristics will be compared between the two groups using Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. A multivariate logistic regression will be conducted to determine independent associations between stone-free rate and certain candidate predictors chosen a priori, including patient position, number of stones, and stone volume.

9.3.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Stone free rates for each laser will be analyzed using the Kruskal-Wallis statistical test. Multiple multivariate regression will also be used to control for stone size, operative time, and other potential confounders.

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Fragmentation speed, energy utilization, lasing activity, operative time, lasing time, lithotripsy time, and treatment time will be analyzed using Kruskal-Wallis statistical tests and multivariate regression to predict differences in levels of renal-damage associated biomarkers.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

The standard informed consent process for research outlined in SOP HRP-090 will be followed.

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Subjects will be recruited from Dr. Mantu Gupta's practice. Patients will be recruited during initial presentation to the office. Consent will be obtained at the initial office visit when decision to proceed to surgery has been made.

Potential subjects will be informed of the study at their preoperative visit (see above point) and may sign the consent at that time if they feel comfortable. If subjects require time for further contemplation, the consent may be signed on the day of surgery in the preoperative area (prior to administration of any anesthesia). This gives potential subjects at least 24 hours to consider the study and review the consent form.

Given the simplicity of the nature of subject involvement, we anticipate that no more than 5 minutes will generally be required to explain the consent form. However, longer and more extensive discussions will be available to those who request or require. All potential subjects will be verbally informed that their participation is completely optional and that their decision of whether or not to participate does not impact their care in any manner. Subjects will be asked to verbally repeat and summarize their involvement in the study. A copy of the consent form will be provided to the subject directly after signing the form.

10.1.2 CONFIDENTIALITY AND PRIVACY

The data will be housed in Mount Sinai's REDCap database. The data is anonymous, and no identifiers are collected. The data will be stored with protected passwords. The data will be reported to the sites in aggregate and anonymized. The publication will also not mention any center by name. The results in the publication will be in aggregate form and anonymous.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

The data will be deleted 6 years after publication, per regulations. Data will not be shared with any outside organizations. Urine specimens will be stored with identifiable information removed. After this removal, samples may be the information and/or samples may be used for future research studies or shared with other research teams for future research studies. Subjects will not be informed of the details of specific research that is done with the specimens.

10.1.3.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the research staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCAP, a password protected, HIPPA compliant database.

The data safety will be monitored by the PI

10.1.3.2 STUDY RECORDS RETENTION

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Study documents will be retained until at least 6 years have elapsed since the formal discontinuation of clinical development of the study intervention.

10.1.4 PROTOCOL DEVIATIONS

The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

11 FUNDING

There is no funding for this study.

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