Vanderbilt University Medical Center
Department of Urologic Surgery
A-1302 Medical Center North
Nashville, TN 37232-2765

PROSPECTIVE RANDOMIZED DOUBLE BLIND CLINICAL TRIAL TO COMPARE HOLMIUM LASER LITHOTRIPSY WITH AND WITHOUT MOSES LASER TECHNOLOGY FOR THE URETEROSCOPIC TREATMENT OF NEPHROLITHIASIS

Principal investigator: Nicole Miller, M.D., Associate Professor
VUMC Department of Urology
A1302 Medical Center North
1161 21st Avenue, South
Nashville, TN 37232-2765

Identifiers:	NCT04505956
Unique Protocol ID:	Moses Ureteroscopy RCT
Brief Title:	A Comparison of Ureteroscopic Treatment of Nephrolithiasis With and Without Moses Technology

Vanderbilt University Medical Center
Department of Urologic Surgery
A-1302 Medical Center North
Nashville, TN 37232-2765

Table of Contents:

Background

Flexible ureteroscopy is characterized as first-line therapy for renal stones < 2 cm in size (1,2). Holmium: YAG laser remains the preferred energy modality to break stones of this size into fragments small enough to remove or pass spontaneously through the ureter (2). Advances in the understanding of laser energy delivery have led to the recent commercialization of the "Moses Effect" – the creation of vapor bubbles/cavities between the laser fiber tip and the target through which laser energy can more efficiently travel (3). Lumenis was the first to optimize this laser phenomenon and market it as "Moses Technology" in their Lumenis Pulse™ P120H laser system.

There is ongoing debate on the optimal means of laser stone fragmentation, and Moses technology is the latest advancement to raise questions regarding clinical utility. To date, there are limited clinical data obtained through rigorous study methodology. In addition, knowledge gaps remain regarding the effect of Moses technology on other clinically meaningful outcomes such as stone-free rate.

Therefore, we propose a multi-center, prospective, randomized, double blind clinical trial to further assess the effect of Moses technology for lithotripsy. We aim to study a broader range of outcomes which will be facilitated by being the largest study to date. We also aim to study novel outcomes such as grading retropulsion and visibility by independent blinded review as well as effects of Moses technology on reducing surgeon perceived workload using the NASA Task Load Index (NASA-TLX)(4,5).

1.0 Rationale and Specific Aims

The purpose of this study is to evaluate the potential of Moses laser technology to reduce operative time compared to non-Moses settings for ureteroscopic treatment of nephrolithiasis.

Our primary objective is to compare total operative times between Moses holmium laser lithotripsy and non-Moses holmium laser lithotripsy in the ureteroscopic treatment of renal stones using a dusting technique. Our secondary objective is to evaluate Moses technology to reduce stone retropulsion during holmium laser stone fragmentation.

We hypothesize that the Moses laser technology will significantly decrease total operative time for treatment of renal stone burden totaling 8-20 mm in diameter.

2.0 Animal Studies and Previous Human Studies

Initial preclinical studies by Sero Andonian's group demonstrated significantly reduced stone retropulsion and higher stone ablation volume with Moses technology, leading to the conclusion that the system allows more efficient laser lithotripsy (6). Further work by this group using a stone simulator supported these findings. There was decreased retropulsion and decreased procedure duration in both the dusting and fragmentation models. In the fragmentation model, the decrease in procedural time was approximately 35% (13.9 min versus 9.1 min) (7).

Initial human studies by Mullerad et al. also showed that laser lithotripsy with Moses technology utilized laser energy in less time for stone fragmentation: 10.0 (2.6-15.0) min vs 6.0 (2.8-13.0) min (8).

Nonetheless, not all measures of outcomes have been supportive. Stern and Monga evaluated the cost effectiveness of Moses technology in their own cohort of 40 patients who underwent standard laser lithotripsy by comparing the savings achieved from a 35% projected decrease in procedure time against the cost of the Moses laser fiber and machine. Mean stone size was 10.2 mm in this group of patients, and mean lasing time was 3.0 minutes. While a significant positive association was seen between stone size and laser time, cost analysis failed to show a benefit in using Moses technology across sizes (9).

A randomized, double blind clinical trial evaluating Moses technology in 66 patients undergoing ureteroscopy was presented as a 2018 European Association of Urology abstract. While this single center study demonstrated safety and reduced fragmentation time as well as procedure time using Moses technology, it did not show a significant difference in stone-free rates (10). Their study is yet to be published as a manuscript.

3.0 Inclusion/Exclusion Criteria

Inclusion criteria:

- Solitary renal stone 8 to 20 mm in size or in the case of multiple stones the conglomerate diameter (additive maximal diameter of all stones on axial imaging of computed tomography) of 8-20 mm is required
- Must be a suitable operative candidate for flexible ureteroscopy per urologic guidelines (1)
- Must be 18 years or older
- Must be able to give consent

Exclusion criteria:

- Concomitant stones in the ureter

- Prior ipsilateral upper urinary tract reconstructive procedures or history of ipsilateral ureteral stricture
- Prior radiotherapy to the abdomen or pelvis
- Neurogenic bladder or spinal cord injury
- Pregnancy
- Untreated UTI

Attending surgeons participating in the study at must be urological surgeons specializing in kidney stones.

4.0 Enrollment/Randomization

The trial will be a prospective, randomized, double blind study of patients with renal stones 8-20 mm in size located at or above the level of the ureteropelvic junction. This is a multi-institutional study and will collaborate with the Cleveland Clinic, Columbia University, Duke University, University of California San Diego, Indiana University, and Mayo Clinic (Arizona) using an identical protocol. Total enrollment will be limited to 300 patients for the study with each site having a goal of up to 100 patients, understanding that some sites may recruit less than their goal. Each site is responsible for its own IRB approval. Ureteroscopic treatment of renal calculi is a standard of care treatment approach, and in the course of participating in this study no treatments will be performed that are not considered standard of care.

Patients will be identified based on clinic visits or hospital admission.

Patients will be randomized on a 1:1 basis to standard holmium laser lithotripsy dusting settings or holmium laser lithotripsy using Moses technology. All surgeons will be blinded to the randomization and only the laser technician will know the randomization. The randomization will be stratified by centers and also by renal stone size (8.0-12.0mm, 12.1-16.0mm, 16.1-20.0mm). Block sizes of 2, 4, and 6 will be used within each stratum to enhance blinding. The randomization system will be developed using R, implemented using RedCap and maintained in the Center for Quantitative Sciences server at Vanderbilt.

5.0 Study Procedures

Procedures performed in this study that are standard of care:

Patients will be identified based on clinic visits or hospital admission. All patients will be counseled on standard treatment options – extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL) and ureteroscopy (URS). The discussion regarding treatment options and subsequent care will not

deviate from routine care. Those selecting URS will be enrolled to have data collected prospectively. Patients will be consented prior to surgery for collection of demographic, disease, perioperative, and postoperative data. Abdominopelvic computed tomography (CT) will be used to delineate pre-operative stone size, with measurements captured in greatest axial and coronal dimensions. A preoperative abdominopelvic CT will be obtained if one is not available as clinically indicated per urologic guidelines (1).

Patients will have flexible URS performed in standard fashion, without deviation from the standard of care. The patient will be brought to the operating room and given general or regional anesthesia per anesthesia and patient preference. The patient will be placed in lithotomy position and prepared and draped in standard fashion. Rigid cystoscopy will be performed and a flexible guidewire will be placed through the ipsilateral ureter to the kidney under fluoroscopic guidance. A second wire will be placed at the discretion of the surgeon. Ureteral dilation will be performed at the discretion of the surgeon. A ureteral access sheath will be used at the discretion of the surgeon. Flexible URS and holmium laser lithotripsy will be performed using a dusting technique for stone fragmentation. For all patients, a Moses laser fiber will be utilized.

Laser settings will be at the surgeons' discretion but will be within the range identified as standard for dusting technique (between 0.2-0.5 J and 40-120 Hz). Moses laser technology will be utilized in distance mode as allowed by the machine when frequency is less than 80 Hz. The short pulse setting will be utilized for non-Moses settings. A representative stone fragment will be removed and sent for stone analysis. An additional fragment may be sent for culture at the discretion of the surgeon. Adequacy of dusting will be defined as stone fragments smaller than the laser fiber diameter. A ureteral stent will be placed at the conclusion of the surgery. A string will be left on the stent at the discretion of the surgeon. Post-operative medical therapy will be an alpha receptor blocker to induce ureteral relaxation if not contraindicated for allergy, cataracts, or history of adverse reaction. Additionally, standard postoperative pain medications will be prescribed at the discretion of the treating surgeon.

The stent will be maintained for 4 to 10 days after surgery. Imaging studies will be performed at 6 weeks postoperatively; post-operative imaging will be a CT abdomen/pelvis (low dose where available) to assess for stone-free rate, development or persistence of hydronephrosis/obstruction, and need for ancillary procedures.

Procedures performed in this study that are specific to research:

Attending surgeons will complete a survey at the end of the procedure to confirm their blindedness and predict whether Moses settings were utilized. The survey will also include the NASA-TLX to measure surgeon workload (11). The principal and sub-investigators (attending surgeons) completing the survey will not have access to individual survey responses prior to data analysis.

Representative video clips of stone dusting will be obtained for blinded video review. All other procedures in this study are performed per standard of care.

Data points**:**

Demographic fields that will be obtained preoperatively include age, race, gender, ASA (American Society of Anesthesiologists) score (for comorbidity assessment), height, weight, body mass index (BMI), and prior stone disease. Disease fields that will be obtained include stone size (maximal axial and coronal dimensions), degree of hydronephrosis (mild/moderate/severe), and prior ureteral stenting or nephrostomy tube placement.

Perioperative fields will include total operative time, procedure time, laser time, laser fiber size, settings of lithotripsy (rate, energy), total laser energy used, anesthesia time, type of anesthesia, use of active fragment extraction (beyond that for analysis/culture), 1st assist skill level, use of ureteral access sheath, intra-operative complications, and treatment on any anticoagulation.

Postoperative fields will include length of hospitalization, postoperative complications, stone composition, need for ancillary procedures, stent duration, and stone-free status on postoperative CT imaging.

The degree of intra-procedure stone retropulsion and visibility will be assessed using a Likert scale by blinded video review consisting of 3 individuals. Adequacy of dusting will be graded as a binary variable. Video clips comprising the first 20 seconds and the last 20 seconds of dusting should be recorded. Blinded reviewers will be surgeons who specialize in ureteroscopy and are not employed by a study center.

6.0 Risks

The risks of participating in the study are the same as that of ureteroscopy offered as standard of care. These risks include pain, bleeding, infection, trauma to the urinary tract, and stricture development. Infection may be severe and life threatening in the form of sepsis requiring ICU hospitalization. Trauma to the urinary tract and/or stricture development may be severe and require future procedures. Loss of renal function may be seen as a result of trauma to the

urinary tract, stricture development and any consequent procedures. There may be unknown or unanticipated adverse effects.

7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Adverse events will be monitored for by key study personnel at VUMC from both patient reported data and review of electronic medical records for phone calls, emergency room visits, hospital admissions, re-operations and clinical visit notes.

The principal investigator and/or research team member will report any adverse event to the IRB within 7 days of awareness. A data monitoring committee will not be used. Participant safety will be protected by standard of care for the surgical procedure which includes post-discharge follow-up in clinic 6 weeks after the procedure and a non-contrast CT abdomen/pelvis. The principal investigator and other key study personnel will monitor any unanticipated problems during the standard of care follow-up period and assess all safety and efficacy data.

Regarding other institutions involved in the study, each institution will be required to monitor for adverse events and report to their individual IRBs as well as VUMC at the same time. VUMC will then inform other participating cites of the serious adverse event or unanticipated problem via email communication immediately. These communications will be de-identified to protect individual patient information at a specific site. It is the responsibility of each individual study site to report the event or problem to their respective IRB as well as assess for similar adverse events or unanticipated problems.

8.0 Study Withdrawal/Discontinuation

Subjects would be withdrawn from the study if their anatomy complicates the assigned laser settings or intraoperatively, access is unobtainable in a retrograde fashion. Additionally, participants will be withdrawn if staged ureteroscopy is deemed necessary intraoperatively (>1 ureteroscopy for the treatment of the ipsilateral stone burden). Subjects may withdraw from the study at any time.

9.0 Statistical Considerations

Power:

Hypothesizing a 6 minute decrease in total operative time for the Moses laser group, a sample size of 146 patients per group across all sites will have 80% power to detect a 20% decrease in the total procedure time. If a 5% dropout rate is assumed, the total sample size will be 300 patients. Mean operative time

for dusting using non-Moses settings was estimated as 35.9 minutes +/- 17.8 min based on results from a previous dusting trial (12).

Data Management:

The electronic data will be stored in the REDCap (Research Electronic Data Capture) application (13,14). REDCap is a stand-alone system with no interaction or connectivity to other systems, and the database is located behind the VUMC firewall. Users must have a VUMC provided ID/password to connect to REDCap and their ID must be specifically authorized in order to access an individual study's data. All changes to the data, and each "record viewed" is logged back to the individual ID with a timestamp. When the case report forms are configured, each field has an attribute that can be set to flag it as an "identifier". This "identifier" is used by REDCap to control certain actions related to the field. REDCap also has several built-in functions to control the exporting of identifying information. Individual users are each granted specific export rights, including – None, De-Identified, and Full. Additional export de-identification options include removing identifiers and dates, hashing IDs and date shifting. Centers will be put into Data Access Groups so that they only have access to their own data and not that of other sites. The data center (VUMC) will be the only center will access to the full dataset.

Statistical Analysis:

Intention-to-treat analysis will include all randomized subjects. Demographic data and pre-operative and post-operative data for each treatment group will be summarized using median and quartiles (continuous variables) and frequency and percent (categorical variable). Baseline data will not be compared across treatments as this is a randomized study.

The primary outcome is total operative time, and it is assumed to have a strong correlation with the stone size. A linear regression model will be fit with total operative time as the response variable and the treatment (Moses vs non-Moses) and stone size as the main covariates. An interaction term between the treatment and total operative time will be included in the model to allow for treatment effect estimation at a specific value of stone size. Using this model, we will be able to estimate the difference in total operative time with a 95% confidence interval at a given stone size and if the treatment effect is uniform across stone size. Statistically significant treatment effect on the primary outcome is required to conclude treatment effect.

The secondary outcomes (stone retropulsion and visibility) will be analyzed with the same regression model. Factorial ANOVA will be used to determine any

interaction between Moses utilization and stone size on workload as measured by NASA-TLX. Surgeon prediction of Moses utilization will be compared to the actual setting using chi-squared tests. Stone free rates and complications will be compared using Fisher's exact test. Odds ratios and a 95% confidence interval will be used to quantify treatment-effect difference on these endpoints.

An interim analysis will be performed using a group sequential design to assess if the study can be stopped early. This will be performed at enrollment milestones of n=150 and n=230.

10.0 Privacy/Confidentiality Issues

Data will be collected and stored within REDCap (Research Electronic Data Capture). Only key study personal listed as the principal investigator, study coordinator and research-clinical roles will have access to the research information and video recordings. The principal investigator and study coordinator will have access to the medical record numbers and unique study identification numbers for each participant. Only the study coordinator and research-clinical roles will have access to the surgeon survey responses; the principal investigator and those listed as sub-investigators will not have access to this data prior to data analysis. Video recordings will be de-identified when stored in an encrypted drive and will be accessible only by key study personnel. De-identified video recordings will be sent to blinded reviewers using Secure File Transfer services.

Consent forms will be secured in a study binder and stored in a locked office. Responses to surgeon questionnaires will be annotated into REDCap and stored in a study binder which will be located in a locked office. At the completion of the study, all contents within the study binder including consents and questionnaires will be destroyed in a secure fashion per hospital policy for HIPAA compliance.

Recorded video will include only intracorporeal image frames of the renal pelvis. There will be no patient identifying information in the video clips such as external anatomy/features, PHI, date of surgery, etc. Recorded video clips will only be labeled by the participants' unique study ID number and blinded reviewers outside of VUMC will only have that label for identification.

11.0 Follow-up and Record Retention

Each patient in the study will be followed for 6 weeks after the operation. It is anticipated the data collection will take 30 months to complete, and another 12 months to analyze the data. The principal investigator will maintain the information indefinitely in a password protected, encrypted database. All

identifiers will be destroyed 4 years after the study initiation, or 2 years after data collection is complete, whichever is sooner. Video will be destroyed upon completion of data analysis except for select de-identified clips to be used for study presentation purposes.

13.0 References

1. Assimos Dean, Krambeck Amy, Miller Nicole L., Monga Manoj, Murad M. Hassan, Nelson Caleb P., et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART II. Journal of Urology. 2016 Oct 1;196(4):1161–9.

2. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. European Urology. 2016 Mar 1;69(3):475–82.

3. Ventimiglia E, Traxer O. What Is Moses Effect: A Historical Perspective. Journal of Endourology. 2019 Mar 20;33(5):353–7.

4. Law KE, Lowndes BR, Kelley SR, Blocker RC, Larson DW, Hallbeck MS, et al. NASA-Task Load Index Differentiates Surgical Approach: Opportunities for Improvement in Colon and Rectal Surgery. Annals of Surgery. 2018 Dec;1.

5. Dias RD, Ngo-Howard MC, Boskovski MT, Zenati MA, Yule SJ. Systematic review of measurement tools to assess surgeons' intraoperative cognitive workload. Br J Surg. 2018 Apr;105(5):491–501.

6. Elhilali MM, Badaan S, Ibrahim A, Andonian S. Use of the Moses Technology to Improve Holmium Laser Lithotripsy Outcomes: A Preclinical Study. J Endourol. 2017 Jun 1;31(6):598–604.

7. Ibrahim A, Badaan S, Elhilali MM, Andonian S. Moses technology in a stone simulator. Can Urol Assoc J. 2018 Apr;12(4):127–30.

8. Mullerad M, Aguinaga JRA, Aro T, Kastin A, Goldin O, Kravtsov A, et al. Initial Clinical Experience with a Modulated Holmium Laser Pulse—Moses Technology: Does It Enhance Laser Lithotripsy Efficacy? Rambam Maimonides Med J [Internet]. 2017 Oct 16 [cited 2019 Oct 25];8(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5652929/

9. Stern KL, Monga M. The Moses holmium system - time is money. Can J Urol. 2018;25(3):9313–6.

10. Ibrahim A, Fahmy N, Carrier S, Elhilali M, Andonian S. 990 - Double-blinded prospective randomized clinical trial comparing regular and moses modes of holmium laser lithotripsy: Preliminary results. European Urology Supplements. 2018 Mar 1;17(2):e1390.

11. Hart SG, Staveland LE. Development of NASA-TLX (Task Load Index): Results of Empirical and Theoretical Research. In: Advances in Psychology [Internet]. Elsevier; 1988 [cited 2019 Dec 16]. p. 139–83. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0166411508623869

12. Humphreys Mitchell R., Shah Ojas D., Monga Manoj, Chang Yu-Hui, Krambeck Amy E., Sur Roger L., et al. Dusting versus Basketing during Ureteroscopy–Which Technique is More Efficacious? A Prospective Multicenter Trial from the EDGE Research Consortium. Journal of Urology. 2018 May 1;199(5):1272–6.

13. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009 Apr;42(2):377–81.

14. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics. 2019 Jul;95:103208.