Protocol:

"Laser lithotripsy during ureteroscopy - Holmium vs Thulium.

A clinical prospective randomized trial of effectiveness and safety."

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The authors' contributions to the study:

Ø Ulvik is the project manager and is responsible for the overall progress of the study. He will write the study protocol, making the data registration forms, patient information and consent forms, apply for approval by The National Committees for Research Ethics in Norway and The Data Protection Authorities at Haukeland University Hospital (HUH). In addition, Ulvik will apply for registration in the clinical research database for randomized trials, ClinicalTrials.gov. Ulvik will also be doing the ureteroscopies and follow-up in the study patients, sampling data and do the statistical analyses, and write the draft of the manuscript. P Gjengstø will do the ureteroscopies, follow-up, sampling of data and contribute to the design and content of the manuscript in addition to critical review of the final version. C Beisland will contribute to the design and content of the manuscript in addition to critical review of the final version. In addition, he will contribute to the data analyses.

Background:

Until now, laser lithotripsy during ureteroscopy (URS) has been performed using Holmium: yttrium-aluminum-garnet laser. Recently, a new Thulium laser has been introduced. The pulsed infrared light emitted by the Thulium laser has a wavelength of 1940 nm which is close to the water absorption peak, and the energy delivered by the Thulium laser is therefore highly absorbed by water. High water absorption corresponds to low threshold for tissue ablation and stone lithotripsy [1]. The Thulium laser is therefore expected to be very efficient at disintegrating stones. Previous studies have predicted Thulium laser lithotripsy to be up to four times faster than Holmium laser lithotripsy using the same energy settings [2]. In theory, as the threshold for tissue ablation is low, ureteral lesions caused by unintentional laser firing at the mucosa may result in less bleeding than with holmium lasers as bleeders are instantly coagulated. In addition, the Thulium laser has the advantage of having smaller laser fibers enabling better irrigation during URS.

As the first hospital in Europe, HUH got access to the new Olympus Soltive Premium SuperPulsed Thulium Laser System in June 18th 2020. To date, approximately 30 procedures have been performed using this laser at our hospital, and the preliminary results seem promising.

The laser has been shown to be a highly efficient tool in the treatment of both ureteral and renal stones even at very low energies. Stone burden up to 3.2 cm has been effectively cleared. Our impression is that the laser produces significantly smaller fragments and finer dust-particles compared to the Holmium laser in shorter time. Fragmenting at a setting of 0.6 - 0.8 J at 30 Hz (18 - 24 W) produces dust and disintegrates stones faster than dusting at 0,1 - 0,2 J at 200 - 240 Hz (20 - 48 W), even though the latter setting results in finer dust. Complete disintegration of a 1 cm stone at 0,6 J at 30 Hz has been achieved in less than 20 minutes.

A remarkable characteristic noted when breaking ureteral stones at low energy, is the absence of retropulsion.

No significant intraoperative complications have been registered so far. However, in a few cases small superficial mucosal laser lesions were noted. No bleeding impairing endoscopic vision has been registered, and adequate vision was maintained in all without the use of irrigation pumps. Insertion of a JJ-stent post endoscopically also seems to be required in a few cases only.

Although the preliminary results of the new Thulium laser look promising, there are no clinical randomized trials comparing it to the Holmium laser, which is the current standard laser used for URS lithotripsy.

Aims of the study:

The primary aim of the study is to compare the stone free rate (SFR) following URS lithotripsy with Holmium and Thulium lasers. SFRs will be compared both for ureteral stones, renal stones and ureteral and renal stones in total.

Secondary aims are to compare the results of the two lasers in terms of operating times, intraoperative complications, postoperative complications and the rate of post endoscopic JJ-stenting.

Hypothesis:

1. The SFR, defined as no residual fragments detected on CT scan 3 months after the URS, is higher following lithotripsy with Thulium laser compared to Holmium laser. The corresponding H_0 is that *"there is no difference in SFR following laser lithotripsy with the two lasers."*
2. Operating time following Thulium laser lithotripsy is shorter compared to Holmium laser. *H_0: "There is no difference in the operating time between the two laser machines."*
3. There are less intraoperative complications during Thulium laser lithotripsy compared to Holmium laser. *H_0: "There is no difference in intraoperative complications between the two laser machines."*
4. There are less postoperative complications (infections, readmissions, strictures) during Thulium laser lithotripsy compared to Holmium laser. *H_0: "There is no difference in postoperative complications between the two laser machines."*
5. Fewer patients will need post endoscopic insertion of JJ-stent following Thulium laser lithotripsy compared to following Holmium laser lithotripsy. The corresponding H_0 is that *"there is no difference in the frequency of post endoscopic JJ-stent placement following laser lithotripsy with the two lasers."*

Study design:

The study is planned performed as a prospective randomized trial. All patients ≥ 18 years scheduled to URS lithotripsy at the day surgery unit at HUH are invited to be enrolled in the study. After written informed consent, patients are randomized to URS lithotripsy with either Holmium laser or Thulium laser.

Randomization:

The randomization is performed electronically with the same number of patients in each group. The results of the randomization are being kept in sealed and consecutively numbered envelopes that is opened just before starting the endoscopic procedures in each patient.

Patients and data sampling:

All patients ≥ 18 years scheduled for URS lithotripsy at the day surgery unit at HUH are basically eligible for inclusion in this study. Patients with either ureteral stones, renal stones or both can be included. The number of patients/procedures needed to be included in the study is specified in the Power analysis-section below.

The following data need to be registered:

- *Preoperative status:* Age, sex, ASA-status, indication for surgery, earlier surgery for same stone, stone status, acute/planned surgery, prestenting-status, infection.
- *Peroperative characteristics:* Randomization status, primary surgeon, antibiotic prophylaxis, operating time, need for safety guide wire and access sheath, type of endoscope (semi-rigid/flexible), balloon dilatation, impacted stone, successful access to the stone, laser modality, laser settings, laser time and energy used, dusting or fragmentation, retrieval of fragments or left for spontaneous passage, surgeon's assessment of post

	endoscopic stone free status, complications, placement of JJ-stent.
• *Postoperative status:*	Length of hospital stay, immediate complications that need urgent treatment, complications after discharge requiring readmission, 3-months follow-up with CT scan (SFR, stricture rate).

The data will be plotted in a registration form which will be available both electronically and on paper. If paper form is used, the data will be registered electronically subsequently and the paper-form maculated. Completed registration-forms are transferred to a SPSS database for statistical analyses.

The registration-forms and the database will be stored at Helse-Bergen's scientific and research server in a designated file assigned from the Data Protection Officer. An ID-Key file combining personal ID to the registration form will be stored at a designated server for this purpose at Helse-Bergen's research servers. Only the project manager (Øyvind Ulvik) will have access to this ID-Key file.

The registration forms and the ID-Key file will be kept on the server for five years after the study has been completed in accordance with the law. After five years the data will be made anonymous in terms of deleting the ID-Key file.

Power analysis:

In an earlier study, we found the 3-months SFR after Holmium laser URS lithotripsy to be 54.2% using a strict definition of *no* residual fragments detected on CT scan [3]. Although this is a strict definition, it leaves no room for personal judgement whether a patient is stone free or not. The definition is therefore suitable for this study purpose.

We expect the Thulium laser to be more efficient in clearing stones than the Holmium laser, with a total SFR of around 80% after URS lithotripsy using this laser.

Comparison of the SFRs between Holmium and Thulium laser will be done using the χ^2-test. An effect size of 0.3 is considered appropriate assuming the SFRs after Holmium and Thulium laser lithotripsy to be 54.2% and 80%, respectively. The α error probability is set to 0.05 and the power (1-β error probability) is set to 0.8. Comparison of the SFRs following URS with the

two lasers with χ^2-test is based on a 2 x 2 table, and in this case with only 1 degree of freedom (Df).

Using G*Power, version 3.1.9.4 for power analysis, the total sample size is calculated to be 88. To compensate for possible non-evaluable patients, a total of 120, i.e. 60 patients in each group, are planned to be included in the study.

Statistical analyses:

Statistical analyses will be performed using IBM SPSS Statistics 25 or higher (IBM, Armonk, NY). A *p*-value < 0.05 will determine statistical significance.

Continuous variables will be compared using independent-samples *t*-tests, or in the cases were a normal distribution is not met, Mann-Whitney U test. Exact chi-squared test and Fisher's Exact test are used comparing categorical variables.

Ethical considerations, ethical approval and patient consent

Holmium laser lithotripsy is the gold standard during URS today and is in use worldwide. Preliminary results with the new Thulium laser seem promising, however, no randomized trials comparing the outcome of the two laser modalities exists. The planned study therefore seems to be highly clinically relevant. In addition, the new Thulium laser is approved for use during endoscopic lithotripsy and the patients should therefore not be exposed to extra risk of harm using this laser.

Applications for approval by The National Committees for Research Ethics in Norway and The Data Protection Authorities at HUH will be sent prior to study start. In addition, the study will be registered in the clinical research database for randomized trials, ClinicalTrials.gov.

All patients eligible for inclusion in the study will receive oral and written information. Participation in the study is voluntarily, and the patient ca choose to withdraw at any point during the study process. Inclusion in the study will only be done after the consent form is signed. The patient information and consent form used for this purpose is obtained from The National Committees for Research Ethics in Norway's website (https://helseforskning.etikkom.no/frister/malforinformasjonsskriv?p_dim=34672).

Laser settings

The laser settings in the two study groups need to be standardized. The following laser settings are suggested as the start-up settings. In the cases of insufficient effect, higher energies can be applied but then need to be registered.

Ureteral stones:	0.4 J at 6 Hz (2.4 watts), long pulse
Renal stones:	0.4 - 0.8 J at 6 - 20 Hz (2.4 - 16 watts) for Holmium and 0.6 - 0.8 J at 30 Hz (18 - 24 watts) for Thulium.

The initial settings for the Thulium laser when treating renal stones are at a higher watt-level compared to the Holmium laser settings, and is therefore expected to be more efficient. However, the fact that the Thulium laser is able to deliver more energy needs to be considered when comparing the clinical outcome of the two lasers.

Study progress

The date for completing the data registration form, patient information and consent form, and application for approval by The National Committees for Research Ethics in Norway is set to 18th of August 2020.

During August 2020 the application form to The Data Protection Authorities at HUH will be sent. Prior to study start the study will also be registered in the clinical research database for randomized trials, ClinicalTrials.gov.

Inclusion of patients and ureteroscopies is expected to start in October 2020, and the inclusion is expected to close during March 2021.

Data analyses and writing a draft is set to spring 2021. Final manuscript ready for submission is planned during the summer 2021.

Funding

No external funding is planned. Hopefully, the project can be completed during regular working hours at Haukeland University Hospital and the University of Bergen.

Conflicts of interest

Øyvind Ulvik is a consultant for Olympus, who was not involved in the design, collection, analyses, interpretation or reporting of the data. The two other authors have nothing to disclose.

Publication of data

The results of the study are planned published as a manuscript in an international urological journal (*Journal of Endourology, Urology or European Urology*). Parts of the results may also be presented at international congresses.

Bergen 05.08.2020

Øyvind Ulvik

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