Protocol:

Temperature profiles during laser activation in ureteroscopic lithotripsy - a prospective clinical study

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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 research database for clinical trials, ClinicalTrials.gov. Ulvik will also be doing the ureteroscopies and follow-up in the study patients, sampling data and take part in the statistical analyses. In addition, he will contribute to the draft and will supervise the writing process of the manuscript.

M Æsøy is, together with Ø Ulvik, the main investigator and will take part in all processes of the study (development of registration forms, performing ureteroscopies and follow-up of the patients, data sampling, statistical analyses). He will also be the first author of the main article, and is responsible for making the draft, revisions and writing the final manuscript.

P Juliebø-Jones will contribute to the data collection, ureteroscopies and follow-up, drafting of the manuscript, revisions 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:

The past 30 years, laser lithotripsy during ureteroscopy (URS) has been performed using Holmium: yttrium-aluminum-garnet laser (Ho:YAG). The Ho:YAG has been considered the *gold-standard* laser for URS because of its versatility, with the ability to break all kinds of stones in the urinary tract as well as tumor- and soft tissue ablation. Development of higher power laser technology has allowed the limits of what can be achieved with URS to be set even higher [1,2]. In comparison to stone fragmentation, techniques such as dusting and popcorning often implement higher power settings (>20 W), and the efficacy associated with different strategies has been the focus of many studies [3-5]. In recent times, the intraoperative safety of URS has gained increasing attention, particularly with regard to high intra-pelvic pressure (IPP) and raised temperature levels [6-9]. The results of such studies include new recommendations for procedural techniques aimed at reducing the risk of complications. One such example is the avoidance of pressurized irrigation pumps [8].
Recently, a new Thulium fiber laser (TFL) has been introduced. With the advent of the TFL, discussion surrounding high temperatures during lithotripsy and resultant thermal damage have been fueled further [10]. Defining safe margins for laser settings is especially important for the TFL as no consensus exists for what is acceptable during URS. In a recent publication, some experts' preferred settings for the TFL during URS were presented, and a variety of different settings was suggested included high power settings as high as 45 Watts [11].
Earlier this year we investigated temperature profiles during URS laser activation with different lasers (TFL and Ho:YAG), laser settings and fiber sizes in a pre-clinical study [12]. We found that the rise in temperature in the renal pelvis was negligible when low settings below 8 Watts were used, even when the laser was activated continuously for 180 seconds. However, applying laser settings of 20 Watts resulted in a significant rise in temperature and the threshold for heat induced cell injury (43^{o}C) was reach and trespassed after approximately 40-45 seconds of continuous laser activation depending on the size of the fiber. Using smaller fiber extended the time before 43^{o}C was reached. These findings need to

be confirmed in clinical studies. However, until then, we expect laser settings ≤ 20 Watts for lithotripsy in the renal pelvis to be safe with regards to temperature.
To date, there are no clinical studies investigating intrarenal temperatures during URS laser treatment. Studying temperature profiles during URS laser activation in patients is therefore of critical importance and highly clinically relevant to define the safety of different laser settings and power.

Aims of the study:

The primary aim of this study is to investigate the temperature profiles in the renal pelvis during TFL laser activation using different settings. To this end, comparison of peak temperatures during laser activation for different settings is the main aim. Secondary aim is trying to define the duration of safe laser activation until the threshold for heat induced cell injury (43^{o}C) is reach.

Hypothesis:

1. Laser activation using low settings is safe regarding intrarenal temperature.
2. The peak temperature in the renal pelvis is higher when high power settings is used compared to when lower settings is used. H_0: *"There is no difference in peak temperatures in the renal pelvis regardless of the laser settings used."*
3. The time before 43^{o}C of intrarenal temperature is reach is longer for low laser settings (if 43^{o}C is reach at all) compared to high settings. The corresponding H_0 is that *"there is no difference in time until 43^{o}C is reached following laser lithotripsy with high and low laser settings."*

Study design:

The study is planned as a prospective clinical trial.

Patients and data sampling:

Patients ≥ 18 years with a ureteral stone (with or without a concomitant renal stone) *and* an indwelling nephrostomy tube scheduled for URS lithotripsy at the day surgery unit at HUH, are invited to be enrolled in the study. Due to the result of the pre-clinical study, a power analysis reveals that a total of 10 patients are considered sufficient for inclusion in the study.

The following data need to be registered:

- *Preoperative status:* Age, sex, ASA-status, comorbidity, indication for surgery, stone status, infection.
- *Peroperative characteristics:* Primary surgeon, antibiotic prophylaxis, operative time, need for safety guide wire, type of endoscope (semi-rigid/flexible), balloon dilatation, impacted stone, successful access to the stone, laser settings, laser time and energy used, temperature measurements, 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 electronical registration forms. Completed registration-forms are exported to a SPSS database for statistical analyses.
The registration-forms and the database will be stored at Helse-Bergen's 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 the pre-clinical study, we found that the peak temperatures when activating the TFL laser continuously for 180 seconds using a 150µm fiber were 26.7°C, 32.8°C and 45.2°C for the laser settings of 0.4J/6Hz (2.4W), 0.8J/10Hz (8W) and 0.2J/100Hz (20W), respectively [12]. The

corresponding baseline temperature before activating the laser were 24.1°C, 24.5°C and 25.3°C.

We expect both the baseline and the peak temperatures to be approximately similar also during URS in real patients as the temperature of the irrigational fluid is the same as in the pre-clinical study (23 °C) [12].

Peak temperatures for different laser settings will be compared using paired-samples *t*-test. Using the peak temperatures for the different laser settings found in the pre-clinical study, the sample size can be calculated for the clinical study assuming the peak temperature will be similar. As the peak temperatures for different laser settings will be compared within the same individual, paired samples *t*-test is used. The total number of patients required for comparison is therefore lower than if peak temperatures were measured for only one laser setting in each patient. In that case independent samples *t*-test would have been the correct test for comparison.

The effect size is calculated to be 4.4 comparing peak temperatures at 2.4W and 8W, and 2.9 comparing peak temperatures at 8W and 20W. The assumed peak temperatures for 2.4W, 8W and 20W are 26.7°C, 32.8°C and 45.2°C, respectively. The corresponding standard deviations are assumed to be 0.8, 1.6 and 4.9, respectively. The α error probability is set to 0.05 and the power (1-β error probability) is set to 0.8.

Using G*Power, version 3.1.9.4 and IBM SPSS Statistics 27 for power analysis, the total sample size is calculated to be 3 when comparing 2.4W and 8W and 4 when comparing 8W and 20W. The highest number of these two calculations is considered appropriate to use. To compensate for possible non-evaluable patients, a total of 10 patients are planned for inclusion in the study.

Statistical analyses:

Statistical analyses will be performed using IBM SPSS Statistics 27 or higher (IBM, Armonk, NY). A *p*-value < 0.05 will determine statistical significance.

Peak temperatures between different laser settings will be compared using paired-samples *t*-tests. Wilcoxon test for related samples will be used comparing the continuous temperature profiles for different laser settings. Exact χ^2-test test and Fisher's Exact test are used comparing categorical variables.

Ethical considerations, ethical approval, and patient consent

TFL is emerging as the laser of choice for ureteroscopic lithotripsy, and the laser has been demonstrated to be superior to the current gold-standard Ho:YAG laser regarding clinical outcomes [13]. Despite being in daily use around the world, no consensus exists of what is considered the preferred laser settings and different experts recommend a variety of suggestions [11]. Some of the laser settings preferred by experts exceeds 20W, which are settings found to be associated very high temperatures (> 43°C) [12]. Defining safe laser settings with regard to temperatures therefore seems to be highly clinically relevant. The intra renal temperature is measured continuously during laser activation in the planned study, and laser activation is stopped immediately if the temperature reach 43°C for any laser setting. Participating in this study should therefore not expose the patients to extra risk of harm. The operative time will be extended by approximately 10 – 15 minutes for the patients in whom the ureteral stones *cannot* be pushed back into the renal pelvis for disintegration as the stone must be disintegrated in the ureter *before* temperature measurements can be performed in the renal pelvis in such patients. However, as the URS procedures are performed in general anaesthesia, the extra time caused by the temperature registration is not considered to cause any disadvantage for these patients.

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 can 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).

The URS procedure and follow-up

Only patients with ureteral stones or combined ureteral and renal stones and who has an indwelling nephrostomy catheter are eligible for inclusion in the study.

The URS procedure is performed in general anaesthesia and all patients will have prophylactic antibiotics prior to surgery start, either according to urine culture or current local regime.

The procedure starts with a cystoscopy followed by semirigid URS when considered appropriate. Balloon dilatation is performed on demand. When reaching the stone, this is flushed back into the renal pelvis for disintegration there if possible. In cases where the stone cannot be flushed back into the renal pelvis, the stone is disintegrated in situ before the endoscope is advanced up to the renal pelvis for temperature measurements. Before laser disintegration, the semirigid ureteroscope is changed for a flexible ureteroscope (Olympus V3) that is advanced to the renal pelvis directly or over a guide wire that must be removed as soon as the endoscope is in place. An access sheath cannot be used during this study. Room-tempered (23^{o}C), gravitational irrigation fluid at 60 cm height is used throughout the procedure. Manual pumping should be avoided and should in any case not be performed during the temperature measurements. Under endoscopic vision, a sterilized thermocouple sensor (K-type, same as in the pre-clinical study) is introduced through the nephrostomy tube so that the tip can identified through the side-holes of the nephrostomy tube. The sensors have undergone sterilization. Formal testing by the microbiological department at Haukeland University Hospital has verified this process successfully sterilizes the sensors. The stone is moved to the central renal pelvis for laser disintegration, and a 150µm laser fiber is introduced into the renal pelvis through the working channel of the flexible ureteroscope. At this point the nephrostomy tube is clamped to achieve filling of the renal pelvis and to mimic a normal procedure.

Laser disintegration of the stone is started using the lowest laser setting of 5W continuously for 120 seconds followed by 60 seconds of idling laser. Temperature measurements are maintained continuously during these 180 seconds, with two measurements per second. When the temperature in the renal pelvis has reached base temperature after one series of measurements, the procedure is repeated for the next laser setting. In total, URS lithotripsy are performed for three different settings. If 43^{o}C is reach during laser activation for any of the laser settings, the laser will be stopped immediately and further laser activation with that specific settings will be aborted. Laser activation with subsequent settings will be ready when base temperature is reached.

If stone treatment is not completed at the end of the three series of laser activation and temperature measurements, further stone disintegration will be performed before finishing the URS procedure. A JJ-stent is placed at the end if deemed necessary by the surgeon. The nephrostomy tube is removed when considered appropriate. If a JJ-stent is placed after the procedure, this is removed according to standard routine after 1-2 weeks in the outpatient clinic. Follow-up with CT is performed at 3 months post endoscopically for all patients to assess stone free status and exclude a ureteral stricture in addition to a clinical consultation.

Laser settings

After reaching the renal pelvis with the flexible ureteroscope, the 150µm laser fiber is inserted through the working channel of the scope. The laser is then activated for 120 seconds starting with the lowest settings. Temperature registration is then continued for another 60 seconds. When the temperature in the renal pelvis has returned to basic, the registration is repeated for the next laser settings. A total of 4 series is performed with different laser settings (2.4W, 8W, 20W and 30W) with 150µm laser fiber. Laser activation is immediately paused if the registered temperature reach 43°C. The following laser settings will be used in the study:

5 watts of power: 0.5 J / 10 Hz, short pulse
10 watts of power: 0.5 J / 20 Hz, short pulse
20 watts of power: 0.5 J / 40 Hz, short pulse
30 watts of power: 1 J / 30 Hz, short pulse

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 November 1st 2022.

After achieving ethical approval, application for approval from The Data Protection Authorities at HUH will be sent. Prior to enrollment, the study also needs to be registered in the clinical research database for randomized trials, ClinicalTrials.gov.

Inclusion of patients and ureteroscopies are expected to start in January 2023, and the inclusion is expected to close during June 2023.

Data analyses and writing a draft is set to autumn/winter 2023. Final manuscript ready for submission is planned during January 2024.

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 is not involved in the design, collection, analyses, interpretation or reporting of the data. The 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 equivalent journal). Parts of the results may also be presented at international congresses

Bergen 27.10.2022

Øyvind Ulvik

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