PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF M.D. DEGREE

Efficacy And Safety Of Antegrade Uretroscopic Lithotripsy Versus Retrograde Ureteroscopic Lithotripsy In The Treatment Of Upper Ureteric Stones Measuring > 10 mm In Maximum Dimension And/ Or Impacted Stones. A Randomized Comparative Study

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1. INTRODUCTION/ REVIEW"

Urolithiasis is a commonly occurring pathologic condition of the urinary tract which urologists worldwide are dealing with on daily basis specially with increasing incidence in the last years with the majority of them at upper urinary tract[1].
Upper ureteric stones specially with large size are not likely to pass spontaneously having a chance of 22% versus distal ureteric stones which have a chance of 71% of spontaneous passage[2]. An exact cut-off size for stones that are likely to pass spontaneously cannot be provided; < 10 mm may be considered a best estimate[3].Impacted stones irrespective of size won't pass spontaneously defined radiologically by non movable stone down the ureter on computerized tomography scan for 1 month or inability to pass a guidewire beyond the stone intraoperatively[4]
Upper ureteric stones have been considered a matter of controversy when addressing the most convenient interventional procedure for their treatment taking in consideration the variety of interventional options within the armamentarium of contemporary urology. These options include retrograde URSL, SWL, antegrade URSL and ureterolithotomy, laparoscopic or open, in certain cases[5].
The European Association of Urology (EAU) and American Association of Urology (AUA) guidelines on urolithiasis recommended use of URSL and SWL for treating upper ureteric stones[5,6]. In the recent years there has been a paradigm shift towards increased use of URSL with decreased SWL use for treating upper urinary tract stones[7,8]. It has been postulated that URSL for ureteric stones has higher stone free rate compared to SWL with less need for secondary procedures[9]. Also URSL has a more favorable cost-efficiency profile compared to SWL in treating proximal ureteric stones when chosen as the primary treatment modality[10]. The EAU guidelines on urolithiasis recommends URSL as first option to treat proximal ureteric stones > 10 mm in maximum dimension and to use antegrade access whenever the collecting system is dilated or the retrograde access is inconvenient[5].
Recently many studies assessed the antegrade access for upper ureteric stones making use of different urological endoscopes available with different percutanous tract sizes through the kidney according to used endoscope varying between conventional nephroscopes[11],semirigid ureteroscopes[11], mini nephroscopes[12], flexible nephroscopes[13] and flexible ureteroscopes[4] demonstrating superior stone free rate with percutaneous antegrade access with comparable safety profile with retrograde URSL.

2. AIM/ OBJECTIVES (Maximum 300 words)
We aim to assess the efficacy and safety of antegrade URSL in treating upper ureteric stones >10 mm in its maximum dimension and impacted upper ureteric stones irrespective of its size in comparison to retrograde URSL and evaluate feasibility, adverse events, hospital stay and cost benefit of both techniques.

3. METHODOLOGY:

Patients and Methods/ Subjects and Methods/ Material and Methods (Maximum 1000 words)

"References may be needed"

- **Type of Study**

Randomized prospective study

- **Study Setting**

- Department of urology, Ain Shams University

- **Study Period**

4 years

- **Study Population**

- *Inclusion Criteria:*

- Age > 18 years

- Upper ureteric stones > 10 mm

- Impacted upper ureteric stones defined by non movable stone on CTUT for 1 month or intraoperative failure to pass a guidewire beyond the stone

- *Exclusion Criteria:*

- Unresolved urinary tract infection

- Uncorrected coagulopathy

- pregnancy

- Anatomical abnormalities of the urinary system as horse shoe kidney, pelvic ectopic kidney and ureteric strictures.

- Severe orthopedic malformation hindering prone position or antegrade ureteric access as Kyphosis, scoliosis.

- Pediatric age groups < 18 years

- Ureteric Stent in place

- Concurrent renal stones

- Bladder cancer, upper urothelial tumors and renal tumors.

- **Sampling Method**

Randomization will be done by statistician.

- **Sample Size**

50 patients in either arm, aborted cases will be included.

- **Ethical Considerations**

Patients will be asked to provide a signed written informed consent

- **Study Procedures:**

- **Pre operative work up:**

    - Patients will undergo detailed history taking, physical examination.

- Laboratory work-up:

    - Complete blood count (CBC)
    - Coagulation profile
    - Kidney function tests
    - Liver function tests
    - Urine analysis
    - Urine culture and sensitivity

- Imaging:

    - Patients will undergo plain computed tomography of the urinary tract (CTUT) to be eligible for diagnosis of upper ureteric stone. Upper ureteric stone definition will be the distance from pelviureteric junction to

the proximal border of sacroiliac junction. Impacted stones will be defined as non movable stones for 1 month on CTUT

- Signed informed consent
- Patients who fulfill inclusion criteria will be randomized into 2 groups: Antegrade URSL(A-group), retrograde URSL(B-group).

- **Operative procedure:**

Antegrade URSL- Group A:

1- All patients will be anesthetized by general anesthesia.
2- The patient will be in lithotomy position, cystoscopy will be done, guide wire will be passed to the ureter to bypass the ureteric stone and advanced to the collecting system of the kidney, ureteric catheter (6 Fr, open tip) will pass over the guidewire and an indwelling urethral catheter will be placed in the urinary bladder
3- The patient will be placed in prone position, retrograde pyelography via ureteric catheter will be done, puncture of the collecting system will be done through upper or middle calyx using 18-gauge percutaneous puncture needle guided by fluoroscopy. In case of impacted stones and non passage of guidewire beyond the stone, localization of renal pelvis by 18 gauge Shiba needle in prone position guided by ultrasound will be done then antegrade pyelography will be performed to proceed with calyceal puncture.
4- 0.035 inch PTFE J tip guidewire will be introduced through the puncture needle sheath and negotiated into the ureter down to the stone guided by fluoroscopy.
5- Dilatation of the percutaneous tract using Amplatz dilator 14 fr and its sheath guided by fluoroscopy.
6- Withdrawing ureteric catheter after passage of 0.035 inch PTFE straight guide wire through it to the kidney to act as safety wire guided by fluoroscopy.
7- Passage of Ureteral access sheath 10-12 fr or the Flexible URS itself (Richard Wolf, Boa Vision) on the J tip guidewire then the guidewire will be withdrawn
8- Stone dusting using 200 micron Laser fiber and Lumenis Pulse 50H Laser machine utilizing Holmium Laser
9- Antegrade ureterography via the ureterosocpe will be done at end of stone dusting

10- Passage of 0.035 PTFE straight tip (Boston Scientific) guidewire through the URS to the bladder guided by Fluoroscopy then the safety guidewire will be withdrawn retrogradely

11- Ureteroscope will be withdrawn with ureteral access sheath, if used, along with inspection of ureter up to the kidney

12- Antegrade JJ stent 6fr/26 will be passed antegradely over the straight guidewire to the bladder

13- Amplatz sheath will be pulled out and puncture site closed with a deep mattress suture

- **Retrograde URSL- Group B:**

1- All patients will be anesthetized by general anesthesia.
2- Patients will be placed in supine position
3- Cystoscopy and passage of 0.035-inch straight tip guidewire in the ureter up to the kidney guided by fluoroscopy.
4- 10 Fr dual lumen ureteric catheter is passed along guidewire guided by fluoroscopy to pass a second safety guide wire then ureteric dilatation by Teflon dilators up to 14 Fr then passage of ureteral access sheath 12-14 Fr or the Flexible URS itself ,if the ureter cannot be dilated, on one of the 2 guidewires guided by fluoroscopy then the guidewire will be withdrawn
5- When using flexible ureteroscope, 200 micron Laser fiber will be used to complete stone dusting
6- Retrograde pyelography will be performed at end of procedure then 6fr/26cm JJ stent will be fixed

- **Post operative:**

- In both groups, urethral catheter will be removed after full recovery from anesthesia and blood sample will be obtained on the morning of day 1 post operative for CBC and then patient will be discharged.
- Patients will undergo CTUT after 3 weeks to confirm stone free state before JJ stent removal, stone free state will be defined as no or 2-3 mm stone fragments on CTUT

- **Data collection and deposition:** Data will be collected and deposited in both urology departments.

4. REFERENCES

1- Scales CD Jr, Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012 Jul; 62(1):160-5

2- Morse RM, Resnick MI. Ureteral calculi: natural history and treatment in an era of advanced technology. J Urol.1991;145:263–265.

3- Preminger, G.M., et al. 2007 Guideline for the management of ureteral calculi. Eur Urol, 2007. 52: 1610.

4- Elgebaly O, Abdeldayem H, Idris F, et al. Antegrade mini-percutaneous flexible ureteroscopy versus retrograde ureteroscopy for treating impacted proximal ureteric stones of 1-2 cm: A prospective randomised study. Arab J Urol. 2020;18(3):176-180.

5- Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016;69:475-82.

6- Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART I. J Urol. 2016;196:1153-60.

7- Lee MC, Bariol SV. Evolution of stone management in Australia. BJU Int. 2011;108(Suppl 2):29–33.

8- Ordon M, Urbach D, Mamdani M, et al. The surgical management of kidney stone disease: a population-based time series analysis. J Urol. 2014;192(5):1450–1456.

9- Drake, T., et al. What are the Benefits and Harms of Ureteroscopy Compared with Shock-wave Lithotripsy in the Treatment of Upper Ureteral Stones? A Systematic Review. Eur Urol, 2017. 72: 772.

10- Lotan Y, Gettman MT, Roehrborn CG, et al. Management of ureteral calculi: a cost comparison and decision making analysis. J Urol. 2002;167:1621–1629.

11- Bhat A, Singh V, Bhat M, et al. Comparison of antegrade percutaneous versus retrograde ureteroscopic lithotripsy for upper ureteric calculus for stone clearance, morbidity, and complications. Indian J Urol. 2019;35(1):48-53.

12- Gökce Mİ, Akpinar Ç, Obaid K, et al. Comparison of retrograde ureterorenoscopy (URS) and percutaneous anterograde ureteroscopy for removal of impacted upper ureteral stones >10mm in the elderly population. Int Braz J Urol. 2021 Jan-Feb;47(1):64-70

13- Stavros Sfoungaristos, Ioannis Mykoniatis, Ayman Isid ET AL. Retrograde versus Antegrade Approach for the Management of Large Proximal Ureteral Stones. BioMed Research International, vol. 2016, Article ID 6521461.

Informed consent

Ain Shams University

Faculty of Medicine

Ethical Committee of Scientific research

Informed consent form for parents or guardians of patients who are invited to participate in the research

Research title:

Efficacy And Safety Of Antegrade Uretroscopic Lithotripsy Versus Retrograde Ureteroscopic Lithotripsy In The Treatment Of Upper Ureteric Stones Measuring > 10 mm In Maximum Dimension And/ Or Impacted Stones. A Randomized Comparative Study

Introduction and aim of the work:

Proximal ureteric stones comprise a frequent clinical situation facing urologists with the majority of them requiring interventional procedures. Various procedures have been implemented to address such stones as ureterorenoscopic lithotripsy (URSL), shock wave lithotripsy (SWL) and ureterolithotomy, either laparoscopic or open, in certain cases.

The aim of the present study is to assess the efficacy and safety of antegrade URSL in treating upper ureteric stones >10 mm in its maximum dimension and impacted upper ureteric stones irrespective of its size in comparison to retrograde URSL and evaluate feasibility, adverse events, hospital stay and cost benefit of both techniques which will aid in proper use of either of them in the Egyptian urological society.

Place of work:

Bicentral study to be held at:

- Department of urology, Ain Shams University

Number and Selection of participants:

- Will be 100 participants, 50 patients in each group:
  Group A: antegrade ureteroscopic lithotripsy
  Group B: retrograde ureteroscopic lithotripsy

Plan of the work:

After your consent achievement and fully explained about the steps of research, the subjects of both groups will be subjected to the following:

1. **Clinical parameters:**

   Complete history taking and thorough clinical examination

2. **Laboratory parameters:**

   - Complete blood count (CBC)
   - Coagulation profile (PT, PC, INR)
   - Kidney function tests (Serum crearinine, Na, K and uric acid)
   - Liver function tests (SGPT, SGOT, total & direct bilirubin and albumin)
   - Urine analysis
   - Urine culture and sensitivity

3. **Radiological parameters:**

   Patients will undergo plain computed tomography of the urinary tract (CTUT) to be eligible for diagnosis of upper ureteric stone.

4. **Operation:**

   Group A: antegrade ureteroscopic lithotripsy
   Group B: retrograde ureteroscopic lithotripsy

   Both groups will be operated upon by an expert urologist with tremendous experience in endourilogy.

5. **Post operative:**

   - In both groups, urethral catheter will be removed after full recovery from anesthesia and blood sample will be obtained on the morning of day 1 post operative for CBC and then patient will be discharged.

- Patients will undergo CTUT after 3 weeks to confirm stone free state before JJ stent removal
- our primary endpoint: stone free rate defined by no or stone fragment < 4 mm on CTUT

Benefits expected from the study:

Benefits to the participants:

Treatment of upper ureteric stone and preventing further sequelae of obstructive uropathy

Benefits to the community:

TO assess the efficacy and safety of antegrade URSL in treating upper ureteric stones >10 mm in its maximum dimension and impacted upper ureteric stones irrespective of its *size* which may represent a challenge for retrograde access

Conducting the consent:

The consent will be conducted to the legal guardian or the patient by the investigator, Doctor Mohammad Saad Abdulbaki, urology specialist at Urology Department, Theodor Bilharz Research Institute. Literate individuals will be left to read the consent followed by its explanation by the mentioned investigator, while illiterate individuals will have the consent read and explained to them as well.

Risks and complications:

This research will not expose the patient to further risks or complications despite the standard risks of protocol of Ain Shams University hospitals and Theodor Bilharz Research Institute hospital.

- ***The risk of blood sampling:*** The blood sample will be obtained by a trained, professional nurse using sterile, disposable equipment. The risks of bleeding, bruising, or infection are small, and similar to having blood drawn at your doctor' s office. Some subjects report a feeling of faintness or brief dizziness upon blood sampling. However, the volume of blood (5 milliliters) is small, and will be replaced quickly by your body.
- ***As for antegrade ureteroscopic lithotripsy*:**
  The documented risks of general anesthesia and the endoscopic procedure as

bleeding, hematuria, ureteric trauma, urinary tract infection and urosepsis. These risks can be overcome by:

- ***Anethesia risk:*** thorough preoperative assessment of patient fitness for general anesthesia by experienced anesthesiologist
- ***bleeding:*** in case of significant intraoperative bleeding due to renal puncture and track dilatation, the procedure will be aborted, nephrostomy tube will be inserted and closed for tamponading, hematocrit value will be measured and blood transfusion will be implemented if necessary.
- ***Hematuria:*** in case of mild hematuria, patient will receive intravenous fluids with good oral fluid intake and hemostatic agents as tranexamic acid. In case of persistent significant hematuria despite the abovementioned conservative measures, renal angiography and further intervention radiology may be needed to manage arteriovenous fistula if found.
- ***Urinary tract infection:*** patients with unresolved UTI will be excluded. All patients will receive antibiotic prophylaxis on induction of anesthesia. The procedure will be done under complete aseptic conditions.
- ***Urosepsis:*** multidisciplinary management will be initiated including ICU doctors, empirical broad spectrum antibiotics and intravenous fluids will be given with close monitoring of vital signs, , urine and blood cultures will be obtained and follow up of C Reactive protien and total leucocytic count.
- ***Ureteric trauma:*** at the end of procedure retrograde and antegrade pyelography will be done to ensure integrity of system with no extravasation. In case of trauma noticed during procedure, DJ stent will be inserted either immediately if trauma is significant as perforation and extravasation or at the end of procedure if trauma is of less degree.
- The procedure will be done by a urology expert with tremendous experience in endourology. Any complications will be reported directly to the supervisors of the research and dealt with following the well-established guideline of urology in such situations.

- ***As for retrograde ureteroscopic lithotripsy:***
- The documented risks of general anesthesia and the endoscopic procedure as hematuria, urinary tract infection, urosepsis and ureteric trauma. . These risks can be overcome by:
    - ***Anethesia risk:*** thorough preoperative assessment of patient fitness for general anesthesia by experienced anesthesiologist
    - ***Hematuria:*** patient will receive intravenous fluids with good oral fluid intake and hemostatic agents as tranexamic acid if not contraindicated
    - ***Urinary tract infection:*** patients with unresolved UTI will be excluded. All patients will receive antibiotic prophylaxis on induction of anesthesia. The procedure will be done under complete aseptic conditions.
    - ***Urosepsis:*** multidisciplinary management will be initiated including ICU doctors, empirical broad spectrum antibiotics will be given with close monitoring of vital signs, intravenous fluids will be given, urine and blood cultures will be obtained and follow up of C Reactive protien and total leucocytic count.
    - ***Ureteric trauma:*** at the end of procedure retrograde pyelography will be done to ensure integrity of system with no extravasation. In case of trauma noticed during procedure, DJ stent will be inserted either immediately if trauma is significant as perforation and extravasation or at the end of procedure if trauma is of less dgrees.
    - The procedure will be done by a urology expert with tremendous experience in endourology. Any complications will be reported directly to the supervisors of the research and dealt with following the well-established guideline of urology in such situations.

- ***Plain CT-UT***: It carries the potential risk of radiation exposure.

Reimbursements in cases of risks and complications:

Should the patient get physically injured as a result of research-related procedures, doctor Mohammad Saad Abdulbaki will provide first-aid medical treatment. All complications will be reported to the supervisors of the research.

Alternatives to participating:

In case of refusing to participate in this research, the patient will be followed up and will receive his treatment as planned.

Confidentiality:

You will deal in complete confidentiality, and no one has right to read your patient medical information except the main researcher. After the research is complete, you will be informed regarding your patient `s research results and also further information regarding your patient `s health status.

Right to refuse or withdraw:

Any participant doesn`t have to take part in this research if he/she or want. They may also stop participating at anytime. If you have read this form and have decided to let your patient to participate in this study, please understand that your patient' s participation is voluntary and you have the right to withdraw your consent or discontinue participation at any time without penalty or loss of benefits to which your patient is otherwise entitled. Your decision whether or not to participate in this study will not affect your patient' s medical care. Individual privacy will be maintained in all published and written data resulting from the study.

Contact Information:

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the investigator, Mohammad Saad Abdulbaki at phone number: 050-4160192, mobile number: 01285399230. You can also call the assistant supervisor Dr. Mohamed Hasan at mobile number: 01006763542. If you have any problems or concerns about the study, you can also

call Prof. Mohamed Rafik El Halaby the main supervisor at mobile phone number: 01222127159

You do not have to sign this consent form. But if you do not, your patient will not be able to participate in this research study.

Certificate of consent:

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I ask have been answered to my satisfaction. I consent voluntary to participate in this research and understand that I have the right to withdraw from the research at any time without in any way affecting my patient`s medical care.

- Name of participant:
- Signature of legal guardian:
- Or participant:
- Identity number or finger print: ……
- Date:

I have accurately read or witnessed the accurate reading of the consent to the potential participant. The individual has had the opportunity to ask questions I confirm that the individual has given consent freely.

- Name of researcher: Mohammad Saad Abdulbaki.
- Signature of researcher:
- Date:

This proposal has been reviewed and approved by Ethical Committee of Scientific research, which is a committee whose task is to make sure that research participants are protected from harm.

If you wish to find more about Ethical Committee of Scientific research. Contact:
Name:
Address:
Telephone number:

Statistical analysis

We used the Statistical Package for Social Sciences (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp.) for data analysis. Descriptive statistics were presented as mean ± standard deviation (SD) or as numbers and percentages. Normality was tested using the Shapiro-Wilk test. Data that were normally distributed were presented as mean ± SD, while non-normally distributed data were presented as median and 95% confidence intervals (CIs).

The chi-square (X2) test assessed relationships between categorical variables. For parametric variables, the student's t-test was applied to compare means between study groups, while the Mann-Whitney U test was used to compare medians for variables such as stone size and hospital stay. Fisher's exact test was employed for categorical variables with expected counts < 5. Spearman's correlation was used to analyze relationships between non-normally distributed variables. Binary logistic regression was done to illustrate the odds ratio for complications. A P-value < 0.05 was considered statistically significant.