The Predictive Value of Ureteral Jet Assessment with Ultrasound in Patients Presenting with Acute Renal Colic

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Ureteral jet assessment for the assessment and prognostication of ureteral stones

1.0 BACKGROUND AND RATIONALE

1.1 Study Disease

Nephrolithiasis is a relatively common affliction, affecting upwards of 10% of the US population and accounts for a significant number of Emergency Department (ED) visits [1]. Computed tomography (CT) is the gold standard for evaluation of acute renal colic and diagnosis of urolithiasis [2] [3]. Recently, the use of CT has come under scrutiny due to ionizing radiation and its attendant risks, including skin injury, cataract formation, and most worrisome, solid and hematological malignancy [3][4, 5]. Furthermore, radiation exposure is increased in obese patients [6], a known risk factor for stone disease. Also, as many patients have a life-long affliction with nephrolithiasis[1], the potential for a considerable aggregate accumulation of radiation exposure over their lifespan can be excessive [5, 7, 8]. This patient population, especially those first diagnosed at a young age, would benefit from imaging modalities that do not involve radiation.
Therefore, various efforts are being made to reduce this radiation exposure. One of the most common types of imaging used in the evaluation of nephrolithiasis as an alternative to CT is renal and bladder ultrasound (RBUS) [9]. RBUS has largely been used as an adjunct study in the management of patients with nephrolithiasis[10], especially during pregnancy and in pediatric stone formers. Due to its relatively low cost and lack of radiation, it has the potential to have an increasingly prominent role. The incorporation of ureteral jets assessment (UJA) when using RBUS to assess patients with nephrolithiasis has been shown to have added diagnostic and possibly also prognostic value in the evaluation of these patients[10]. Several studies have attempted to assess the exact role of UJA in patients with nephrolithiasis but have had limited success in delineating its exact role in the treatment algorithm [11].

The prognosis of a ureteral stone as can be conveyed to the patient is based on a historical study from Miller and Kane. In 1999, the authors studied 75 patients with ureteral stones ranging from less than 2mm to 10mm over approximately 6 weeks' time. It was found that smaller, more distal stones pass sooner and that stones <4mm pass 95% of the time, although this may take up to 40 days [13]. Since that time, multiple studies have shown medical expulsive therapy (MET) to be effective for earlier stone passage [14, 15, 16]. No modern investigation of stone passage rates based on size has been performed in the MET era.

1.2 Rationale

Due to the increasing use of CT and concern for radiation exposure, it is important to consider alternative diagnostic imaging modalities. We seek to evaluate patients who present to the Barnes-Jewish Hospital (BJH) ED and to the Urology office with renal colic who have been diagnosed with a ureteral stone. We seek to determine whether the findings on ureteral jet assessment (UJA) by RBUS are predictive of a patient's clinical outcome. Specifically, we seek to

evaluate whether the presence, absence or relative strength of the ipsilateral ureteral jet can predict spontaneous passage versus need for surgical intervention over a 42-day (6-week) time period. As many patients have a life-long affliction with nephrolithiasis[1], the potential for a considerable aggregate accumulation of radiation exposure over their lifespan can be excessive and should not be overlooked [5, 7, 8]. This patient population, especially those first diagnosed at a young age, would benefit from imaging modalities that do not involve radiation.

Evaluating the significance of UJA and RBUS in patients with renal colic will help define the role of this imaging modality, as an alternative to ionizing radiation-based studies. The prognosis of urolithiasis based on UJA will be defined, as well as the natural history of stones managed expectantly. We hypothesize that UJA showing weak or absent ureteral jet will predict obstruction and a higher rate of surgical treatment compared to spontaneous passage. We hypothesize that larger stones will be less likely to pass without surgical intervention.

2.0 OBJECTIVES

2.1 Primary Objective

1. To determine whether use of renal bladder ultrasound (RBUS) with UJA is predictive of spontaneous stone passage versus need for surgical intervention over a 42-day time frame.

2.2 Secondary Objectives

1. To determine whether RBUS with UJA, in conjunction with standard of care history, physical examination and laboratory studies confers the same diagnostic information as the gold standard, non-contrast CT.

2. To determine the natural history and rate and time of stone passage for ureteral stones of differing locations (proximal, mid or distal ureter) and sizes (<2mm, 2-4mm, 5mm, 6-7mm, 9-10mm).

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for study participation:

1. Age 18 and older at the time of consent
2. Willing and able to sign consent
3. CT diagnosis of ureteral stone with a stone burden less than or equal to 10mm

3.2 Exclusion Criteria

Patients must not meet any of the following exclusion criteria to be eligible for study participation:

1. Obstructed solitary kidney
2. Obstructed transplant kidney
3. Bilateral obstructed kidneys
4. Any condition or reason that, in the opinion of the treating physician, interferes with the patient's ability to participate or places the patient at undue risk.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Assignment of unique patient number (UPN)

4.1 Assignment of UPN

Once enrolled in the study, each participant will be assigned a unique participant study number (study ID) which will not include participant's initials. Only research team members will have access to the master key linking participant number to identifiable information, which will remain secure in an encrypted, password-protected file or under two locks. Clinical research data will be identified by participant's unique study number and will also include identifiable information such as subject's name and date of birth. Only members of the research team will have access to participants' research data.

5.0 STUDY PLAN

5.1 Screening and Informed Consent

Subjects will be seen and counseled by either the attending ED physician or their Urologist as part of the normal course of practice. Patients may be approached about study participation as soon as ureteral stone is suspected based on clinical presentation. Following CT diagnosis of ureteral stone, study team will further discuss study participation with the patient and complete the consent process if the patient is willing to participate.

The discussion regarding study participation will take place in a private setting, such as in a private consult room, to maintain confidentiality. HRPO approved consent form will be used to guide the consent process and document participant's consent. During the consent

process, the study team will explain RBUS with UJA, the normal anticipated course of a patient with the represented stone burden, potential risks and benefits of study participation, compensation and study follow-up schedule. Patients will be encouraged to ask questions and discuss the study with family. They will be given ample time to review the consent. It is possible that some participants may be contacted by phone to assess their interest in this study. If the participant expresses interest in the study, informed consent form will be mailed/e-mailed to him/her. This will be done in an effort to allow the patient ample time to read the consent at home, consider the study and discuss it with friends and family. This will not replace the face-to-face consent discussion the research team will have with the patient prior to signing the consent form.

Patients may decline to participate without an impact on their care. They will not be pressured to participate. No study related procedures will take place prior to the completion of the informed consent process and participant signing the HRPO approved consent.

5.2 Study Plan and Procedures

Study RBUS with UJA will be obtained within 10 days following CT diagnosis of ureteral calculus. Ureteral jet data will be documented and patients will be followed prospectively for 42 days at 2 weeks, 4 weeks and 42 days (6 weeks) after diagnostic CT. Specifically, patients will be followed for spontaneous stone passage and will be expected to record date of stone retrieval. If specific date of stone passage is not known, date of standard of care imaging confirming absence of stone(s) will be used as the date of stone passage. If spontaneous stone passage is not achieved, patients will be counseled regarding further standard of care treatment options including surgical stone removal. If surgical intervention is indicated, time to surgical procedure will also be recorded. This patient cohort will be analyzed retrospectively to determine whether RBUS with UJA is predictive of spontaneous stone passage versus need for surgical intervention over a 42-day period.

Interpretation of RBUS and UJA:
Abdominal radiologists will interpret the RBUS research reads. All grey scale and color Doppler examinations will be performed by means of a commercially available unit with a 1-5 MHz phased array transducer or a 1-6 curved transducer. Flow toward the transducer is assigned a red color on Doppler. For grey scale evaluation, the presence or absence of urinary tract stones, size (longest axis in mm) and location- R, L, upper pole, interpolar and lower pole of the kidneys, proximal ureter, distal ureter and bladder- will be documented. The level of the renal pelvis represents the interpolar kidney with upper and lower pole above and below this level. For this study, a urinary tract stone will be termed an echogenic focus that demonstrates either posterior acoustic shadowing and or twinkle artifact on color Doppler images. In addition, presence of hydronephrosis (mild, moderate, and severe) will be documented. For the purpose of this read, hydronephrosis will be defined as such: mild hydronephrosis - urine fills the intra and extra renal pelvis and the major calyces are dilated; moderate hydronephrosis – above + dilatation of the minor calyx with preservation of the renal parenchyma; severe hydronephrosis – above +

thin renal parenchyma. In addition, the presence or absence of hydroureter (proximal ureter, above the iliac bifurcation and distal ureter, below the iliac bifurcation) will be documented. If there is a stone in the renal pelvis, it will be recorded as interpolar kidney and noted as renal pelvis. For any case, if the reader believes that a particular stone is the cause of the participant's symptoms, then this will be noted. This is particularly useful in cases in which there are multiple stones. The bladder will be examined in the transverse plane at the level of the trigone to view both jets simultaneously. All participants will be scanned for 5 minutes. The number of jets from each ureteral orifice will be tabulated over time so that ureteral jet frequency, defined as number of jets per minute, can be calculated. Patients will be categorized into three groups. Group I- no ureteral jets on the symptomatic side; Group II- continuous low-level ureteral jet on the symptomatic side; Group III– ureteral jets similar to nonsymptomatic side.

In order to determine if RBUS with UJA along with clinical data confers non-inferior information compared to non-contrast CT, objective findings such as laboratory data including BMP, CBC, urine analysis and physical exam obtained as part of routine care will be retrieved from the patient's medical record and reviewed retrospectively. Clinical data and RBUS results will be de-identified/coded and the Urologist will be blinded to the CT results. Diagnosis and treatment recommendations will be determined based upon these findings and compared to those attained by CT to assess for congruence. Statistical analysis will be performed to determine non-inferiority between the studies.

Stone size and location based on CT will be recorded at the time of enrollment into the study and time to stone passage will be recorded. All study participants will be followed for stone passage. Time to stone passage will be stratified according to stone location (proximal, mid or distal ureter) and size (<2mm, 2-4mm, 5mm, 6-7mm, 9-10mm).

5.3 Study Follow-up

After study RBUS is obtained, patients will be followed prospectively by telephone call at 2 weeks, 4 weeks and 42 days (6 weeks) from the time of diagnostic CT. They will be followed for spontaneous stone passage, and be asked to keep record of when this occurs. During the 42-day follow up, their course will also be monitored for ED visits, surgical intervention and hospital admissions. All currently available medical records such as Clindesk, Allscripts, Compass, HMED will be reviewed retrospectively to follow participants' clinical course, specifically to determine the need for surgical intervention or spontaneous stone passage. Billing records may also be used to identify patients who underwent surgical intervention based on CPT codes. Evaluation of the patient's emergency room records with a focus on their presenting symptomatology and initial evaluation by the emergency provider will be performed. Any additional laboratory tests and/or imaging obtained during their emergency room or office visit will also be reviewed and collected for study purposes.

Surgical intervention, including ureteral stent or nephrostomy tube placement, ureteroscopy/laser lithotripsy, or extracorporeal shockwave lithotripsy (ESWL) will be instituted, as per standard of care. A follow up telephone call at 2 weeks, 4 weeks and 42

days (6 weeks) from the time of diagnostic CT will be performed in case of care received outside of the Barnes-Jewish Hospital (BJH) system and medical records reviewed for ER visits, hospital admissions and surgical intervention.

5.4 Risks and benefits associated with study participation

The results from this study will not directly benefit the patients who agree to participate, however, we hope they will help define the role of RBUS with UJA as an alternative to ionizing radiation-based studies. Knowledge gained from this study may help us improve our stone management practice.

Participation in this study will not affect the patient's risks associated with the standard of care stone management. There are no risks associated with an abdominal ultrasound. Patient may feel slight discomfort if he or she is experiencing abdominal pain.

Risks associated with the medical expulsive therapy and/or surgical procedure for stone management will be discussed with all participants as part of their clinical care and clinical consent for the procedure will be obtained.

5.5 Duration of Follow-Up

Patients will be followed by telephone call at 2 and 4 weeks and 42 days (6 weeks) after diagnostic CT. They will have a clinic visit with their urologist per standard of care practice.

5.6 Criteria for Removal from Study

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue with study participation, the patient should be removed from the study and the reason(s) for discontinuation documented.

Otherwise, the patient will be followed and evaluated as described.

6.0 DATA AND SAFETY MONITORING

Participation in the proposed study will not pose any risks to the participants beyond what is expected from the standard of care stone management.

The PI will monitor the study for any reportable events from the time of the study RBUS to day 42 post diagnostic CT. All HRPO guidelines for reporting events meeting defined criteria will be followed.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Objectives and Endpoints

Primary Outcome:

To determine if RBUS with UJA is prognostic of stone passage versus need for

surgical intervention:

1. Passage of stone as assessed by patient self-report and/or collection of stone or imaging.
2. Need for further medical attention as collected by chart review and phone interview for ED visit, hospitalization, or need for surgical intervention during the 42-day follow-up period.

Secondary Outcomes:

1. To determine if RBUS with UJA, in conjunction with standard of care laboratory data and history and physical confers non-inferior information compared to non-contrasted CT:
    a. Urologist will review the patient's de-identified/coded history and physical, laboratory studies, and RBUS with UJA and make an assessment and treatment recommendations. The urologist will be blinded to the results of the CT. Comparison will be made between the CT diagnosis and the blinded assessment of the urologist.

2. To determine if the natural history and rate and time of stone passage for ureteral stones of differing locations (proximal, mid or distal ureter) and sizes (<2mm, 2-4mm, 5mm, 6-7mm, 9-10mm):
    a. Assessment of the stone location and size to be conducted by a radiologist.

7.2 Study Design

This is a single institution, prospective study to evaluate the prognostic significance of RBUS with UJA, and its utility in providing non-inferior information compared to non-contrasted CT, as well as to evaluate the spontaneous stone passage rate of ureteral stones. The study will be conducted at Washington University and will enroll approximately 100 participants over two years.

7.3 Data Analysis

Primary objective:
This patient cohort will be analyzed retrospectively to determine whether US with UJA is predictive of spontaneous stone passage versus need for surgical intervention. Kaplan-Meier curve will be used to test time to spontaneous stone passage between the two groups. A chi-square test of independence will be used to test intervention rates between the two groups. A multivariate analysis will also be conducted controlling for such variables as age, gender, BMI, side, size of stone, and stone passage. A Cox-proportional hazards model will be used for time to spontaneous stone passage and logistic regression will be used for intervention.

Due to the unforeseen difficulty of recruitment and the uncertain assumptions of the initial power analysis, an interim statistical analysis is recommended to be performed when the recruitment reaches 50 patients. Based on the results, a decision will be made whether to continue recruitment to the initial 100 targeted patients, adjust the number of targeted patients based on a new power analysis, or to discontinue recruitment. The interim results

should not affect primary independent variables in the study as the radiologist performing the ultrasounds will not have access to the results.

Secondary objective 1:
Statistical analysis will be performed to determine diagnostic and treatment concordance between the two methods. A multivariate logistic regression model will also test patient factors that are associated with discordant results.

Secondary objective 2:
In a prospective manner, they will be followed to determine the natural history of ureteral stones with regard to stone passage. Average time to stone passage for each size category and stone location will be determined. Cox-proportional hazard models will be used to determine significant factors affecting time to stone passage.

8.0 REFERENCES

1. Scales, C., et al., *Prevalence of kidney stones in the United States.* European urology, 2012.
2. Türk, C., et al., *Guidelines on urolithiasis.* European Association of Urology, 2011.
3. Kim, B.S., et al., *Low-Dose and Standard-Dose Unenhanced Helical Computed Tomography for the Assessment of Acute Renal Colic: Prospective Comparative Study.* Acta Radiologica, 2005. **46**(7): p. 756-763.
4. Mancini, J.G. and M.N. Ferrandino, *The impact of new methods of imaging on radiation dosage delivered to patients.* Curr Opin Urol, 2010. **20**(2): p. 163-8.
5. Smith-Bindman, R., et al., *Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer.* Archives of Internal Medicine, 2009. **169**(22): p. 2078.
6. Wang, A.J., et al., *Obesity triples the radiation dose of stone protocol computerized tomography.* J Urol, 2013. **189**(6): p. 2142-6.
7. Sodickson, A., et al., *Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults.* Radiology, 2009. **251**(1): p. 175-184.
8. Broder, J., et al., *Cumulative CT exposures in emergency department patients evaluated for suspected renal colic.* The Journal of emergency medicine, 2007. **33**(2): p. 161-168.
9. Passerotti, C., et al., *Ultrasound versus computerized tomography for evaluating urolithiasis.* The Journal of urology, 2009. **182**(4): p. 1829-1834.
10. Sheafor, D.H., et al., *Nonenhanced Helical CT and US in the Emergency Evaluation of Patients with Renal Colic: Prospective Comparison1.* Radiology, 2000. **217**(3): p. 792-797.
11. Burge, H., et al., *Ureteral jets in healthy subjects and in patients with unilateral ureteral calculi: comparison with color Doppler US.* Radiology, 1991. **180**(2): p. 437-442.

APPENDIX A: Study Schedule of Events

		Post-Enrollment Assessment and Follow-up		
	Within one day of diagnostic CT	**2 weeks post diagnostic CT (+/- 2 days)**	**4 weeks post diagnostic CT (+/- 2 days)**	**42 days (6 weeks) post diagnostic CT (+ 3 days)**
Informed Consent	**X**			
Incl./Excl. Criteria Confirmation	**X**			
RBUS with UJA	**X**			
Demographics[1]	**X**			
Medical & Surgical History[1]	**X**			
Height & Weight[1]	**X**			
Basic metabolic panel[1]	**X**			
Complete blood count[1]	**X**			
Urine analysis and microscopy[1]	**X**			
CT scan[1]	**X**			
Assessments:				
Study related AEs/reportable events		**X**	**X**	**X**
Clinical stone management[1]		**X**	**X**	**X**
Passage of stone		**X**	**X**	**X**

[1] as part of standard clinical care.