First in Human Clinical Trial of Ultrasonic Propulsion of Kidney Stones

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Abbreviations and Acronyms

UW = University of Washington

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Purpose: Ultrasonic propulsion is a new technology using focused ultrasound energy applied transcutaneously to reposition kidney stones. We report what are to our knowledge the findings from the first human investigational trial of ultrasonic propulsion toward the applications of expelling small stones and dislodging large obstructing stones.

Materials and Methods: Subjects underwent ultrasonic propulsion while awake without sedation in clinic, or during ureteroscopy while anesthetized. Ultrasound and a pain questionnaire were completed before, during and after propulsion. The primary outcome was to reposition stones in the collecting system. Secondary outcomes included safety, controllable movement of stones and movement of stones less than 5 mm and 5 mm or greater. Adverse events were assessed weekly for 3 weeks.

Results: Kidney stones were repositioned in 14 of 15 subjects. Of the 43 targets 28 (65%) showed some level of movement while 13 (30%) were displaced greater than 3 mm to a new location. Discomfort during the procedure was rare, mild, brief and self-limited. Stones were moved in a controlled direction with more than 30 fragments passed by 4 of the 6 subjects who had previously undergone a lithotripsy procedure. The largest stone moved was 10 mm. One patient experienced pain relief during treatment of a large stone at the ureteropelvic junction. In 4 subjects a seemingly large stone was determined to be a cluster of small passable stones after they were moved.

Conclusions: Ultrasonic propulsion was able to successfully reposition stones and facilitate the passage of fragments in humans. No adverse events were associated with the investigational procedure.

Key Words: kidney calculi; lithotripsy; nephrolithiasis; ultrasonography; therapies, investigational

THE prevalence of kidney stones continues to increase and it is estimated to affect almost 9% of the American population.[1] The unpredictability of stone movement and resultant pain cause anticipatory fear in many individuals with kidney stones. It is not uncommon for a single stone episode to result in multiple emergency room visits and at least 1 surgical procedure.[2] Annual medical expenditures for urinary stone disease

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has soared to $10 billion, making it one of the most costly urological conditions.[3]

While surgical treatment of kidney stones has evolved from large incision surgery to noninvasive procedures, the current treatment options commonly leave behind residual stone fragments.[4] Studies have shown that while most residual fragments will pass, others may grow and in approximately 20% to 40% of patients lead to symptomatic events such as pain, emergency room visits or additional procedures.[5–9]

Ultrasonic propulsion is a new technology developed to reposition kidney stones and facilitate passage using focused ultrasound energy applied transcutaneously.[10–14] The proposed use is to expel stone fragments while they are small and passable. Other uses include moving larger stones back into the kidney to relieve acute renal obstruction and pain, and help small, newly formed or *de novo* stones pass naturally under controlled conditions rather than waiting for an unpredictable event or until stone growth requires surgery.

The ultrasonic propulsion technology has evolved during 5 years to a clinical prototype device.[10–14] Safety and effectiveness have been demonstrated in a porcine model and IDE (Investigational Device Exemption) was obtained from the United States FDA (Food and Drug Administration) to test the device in humans.[15,16] We report the findings of the first in human clinical trial of ultrasonic propulsion.

MATERIALS AND METHODS

A single center, first in human feasibility study was performed at UW with the approval of the UW institutional review board and the United States FDA through a IDE.

Study Objectives

The primary goal was to demonstrate the ability to reposition stones in the human collecting system. Secondary goals were to 1) demonstrate the ability to move stones in a controlled direction, 2) demonstrate the ability to move small (less than 5 mm) and larger (5 mm or greater) stones, and 3) determine any safety issues or discomfort associated with the investigational procedure. We further investigated the potential impact of stone size, stone location, patient position, treatment voltage and stone type (*de novo* vs fragment) on stone motion.

Investigational Device

The investigational system is essentially a diagnostic ultrasound platform capable of emitting longer duration, slightly higher amplitude focused pulses (VDAS, Verasonics®). A graphic user interface and ultrasound image are displayed on a touchscreen monitor.

The custom derived Push sequence was developed and optimized to work on the same diagnostic probe, a HDI C5-2 curvilinear array (Philips Ultrasound, Andover, Massachusetts) as is used to image the kidney. The operator activates a single Push by touching the stone on the touchscreen or clicking the mouse with the cursor on the stone. The Push sequence occurs between 2 B-mode imaging frames, giving real-time imaging feedback of stone motion. The Push can be applied to any location in the image. Two Push voltage settings are available, including low (50 V) and high (90 V). Low power is used at shallow depths where there is less acoustic attenuation and high power is used at greater depths (7 cm or greater).

Study

Population. Individuals who presented to the UW urology clinic of a single provider from November 2013 until October 2014 were screened. The Appendix shows study inclusion and exclusion criteria.

Because the ultimate application of this technology has a broad scope of use, restrictions on enrollment criteria were minimized. Group 1 (post-lithotripsy) included subjects who had undergone a lithotripsy procedure within the last year with small (less than 5 mm) residual fragments. Group 2 included subjects with small (less than 5 mm) *de novo* stones. Group 3 included subjects with large (5 mm or greater) stones who would undergo planned ureteroscopy the day after ultrasonic propulsion. Group 4 included subjects with large (5 mm or greater) stones who would undergo simultaneous ultrasonic propulsion with ureteroscopy.

Procedure. Subjects underwent screening ultrasound with the investigational device. Subjects then underwent the stone pushing procedure, which was performed by a sonographer and a urologist. Raw ultrasound data and video were recorded. Subject position, and stone location and motion were recorded. Stone motion was classified into 3 types for each Push. Grade 1 reflected no motion, grade 2 indicated that the stone moved within a confined space such as a calyx or rolled back to the same position and grade 3 meant that the stone was translated to a new location (greater than 3 mm). A maximum of 40 Pushes was delivered. Subjects were asked to move to different positions and briefly hold breath to help with targeting.

Safety Assessment. Subjects completed a 10-point pain questionnaire before and after the study. Direct feedback on any sensations was obtained after the first 3 Pushes and as noted thereafter. Research staff contacted the subjects weekly for 3 weeks and reviewed the medical charts during 90 days to assess for renal colic events, stone passage or the need for additional intervention. Ultrasound was done after 4 weeks to rule out hydronephrosis or renal abnormalities.

Exceptions to Study Procedure. Subjects who underwent the investigational study during a ureteroscopic procedure were anesthetized and could not complete the pain questionnaire or provide feedback on any sensation felt during the procedure.

RESULTS

Subject Characteristics

A total of 15 subjects underwent ultrasonic propulsion, including 13 who were awake without sedation