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Update on clinical trials of kidney stone repositioning and preclinical results of stone breaking with one system

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Abstract

Our goal is an office-based, handheld ultrasound system to target, detach, break, and/or expel stones and stone fragments from the urinary collecting system to facilitate natural clearance. Repositioning of stones in humans (maximum 2.5 MPa, and 3-second bursts) and breaking of stones in a porcine model (maximum 50 cycles, 20 Hz repetition, 30 minutes, and 7 MPa peak negative pressure) have been demonstrated using the same 350-kHz probe. Repositioning in humans was conducted during surgery with a ureteroscope in the kidney to film stone movement. Independent video review confirmed stone movements (≥ 3 mm) in 15 of 16 kidneys (94%). No serious or unanticipated adverse events were reported. Experiments of burst wave lithotripsy (BWL) effectiveness on breaking human stones implanted in the porcine bladder and kidney demonstrated fragmentation of 8 of 8 stones on post mortem dissection. A 1-week survival study with the BWL exposures and 10 specific-pathogen-free pigs, showed all findings were within normal limits on clinical pathology, hematology, and urinalysis. These results demonstrate that repositioning of stones with ultrasonic propulsion and breaking of stones with BWL are safe and effective.

1. INTRODUCTION

Stone disease management has changed little in 30 years, and patient care, technology, and cost can be improved.[1] Patients endure pain and anxiety in waiting for spontaneous stone passage. The Urologic Diseases in America project found 65% of kidney stone patients

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filled an opioid prescription and 40% utilized the emergency department (ED) each year including 10% who used the ED more than once to deal with their pain while waiting for definitive management.[2] That management includes ionizing radiation for monitoring even asymptomatic stones, with 70% of stone patients receiving imaging each year, and the majority of these receiving more than one scan. Treatment is not always definitive, and 30% of surgeries need to be repeated.[2] The inefficiencies of ED care, repeat imaging and repeat surgeries make urinary stone disease the costliest non-malignant urologic disease,[2] and the annual cost of care of a stone patient is twice that of patients without stone disease.[3] The ability to noninvasively break stones and expel the fragments in the outpatient setting has the potential to reduce risk, reduce cost, and improve care. This paper is an update on the progress by our NIH Program Project and collaborators to develop and validate an office-based system to find, break, and expel stones and stone fragments from the urinary collecting system to facilitate natural clearance. As such this presentation in the Special Session "Biomedical Acoustics and Physical Acoustics: Shock Waves and Ultrasound for Calculus Fragmentation" established the status in the path to initial clinical implementation, and other papers[4–9] in the session reported progress and approaches to solve technical challenges to tailor the system and technology to be most effective for each individual patient.

2. METHODS

A. INVESTIGATIONAL SYSTEM

Figure 1 shows photos of the University of Washington system called Propulse 1. The operator places the probe on the skin, visualizes the stone with ultrasound (US) imaging and then applies the therapy by a footswitch without interrupting real time US imaging. Propulse 1 uses an SC-50 probe (50 mm diameter) for stone repositioning and an SC-60 (60 mm diameter) probe for stone repositioning and breaking.[10] There is an investigational device exemption (IDE) for human trials of stone repositioning with Propulse 1 and either probe. A second IDE application has been submitted to FDA to add the outputs to break stones. Repositioning is called ultrasonic propulsion and has a maximum of 3 s bursts at 50% duty cycle of up to 2.4 MPa peak negative pressure, to up to 10 minutes. Stone breaking is called Burst Wave Lithotripsy (BWL)[11] and in the IDE application is limited to 20 cycle pulses at 17 Hz for up to 10 minutes at 6 MPa (the maximum attainable with the system and probe) PNP. However, safety tests reported here were performed with a slightly different system which enabled testing at higher pressure levels (30 minutes, 24 cycles, 10 Hz, and 7 MPa PNP).

B. HUMAN STUDIES OF ULTRASONIC PROPULSION

There are four studies discussed, all being conducted under one IDE, to measure feasibility of repositioning stones. Subjects are assessed for inclusion and exclusion criteria and go through the process of informed consent. They are screened by ultrasound to confirm the stone can be seen. If the subjects are awake, they respond to a visual analog pain score before and after screening and the investigational procedure. All subjects are contacted once per week for 4 weeks following for stone passage or adverse events. All receive imaging follow-up after 6 weeks and a chart review at 90 days.

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C. PRECLINICAL STUDIES OF BWL

A 7-day survival study follows the protocol used twice before in our previous ultrasonic propulsion applications.[10,12] Clinical simulation of BWL was conducted by delivering transcutaneous exposures to intact kidneys without stones. Safety assessments included drawing and analyzing blood and urine before and following the investigational procedure and just prior to necropsy 1 week later. A full necropsy was performed and analyzed by a board-certified veterinary pathologist. The studies were conducted following good laboratory practice (GLP) guidelines.

The effectiveness of Propulse 1 was tested in clinical simulation by fragmenting and repositioning stones that were surgically implanted in each bladder of 3 pigs and in the kidney of one of these pigs.

3. RESULTS

A. HUMAN STUDIES OF ULTRASONIC PROPULSION

Table 1 shows a summary of the four human studies. Ultrasonic propulsion has been used safely 65 times on subjects. Ultrasonic propulsion has successfully repositioned stones and clinical benefits have been observed. Studies continue.

B. PRECLINICAL STUDIES OF BWL

Table 2 shows the preclinical results of safety and effectiveness of BWL in animals. The survival study showed no injury to the maximum proposed exposure (7 MPa, 10 Hz repetition rate, 20 cycles, 30 minutes, 350 kHz). Since the exposure time, acoustic pressure and beam width bound our application, we feel these studies demonstrate that our proposed outputs are safe for the proposed human studies. In the effectiveness study, stones were all broken completely in under 10 minutes of exposure. Some pigs were given a total exposure up to 25 minutes, and in no case was gross injury observed. These results are consistent with the results presented by Wang et al.[8] of this session and in review by the Journal of Endourology.[14]

All treatments were monitored with US imaging, and the corresponding video was recorded. In no cases was echogenicity away from the stone seen, which would imply a need to pause the treatment to avoid injury and shielding by a cavitation cloud. May et al. previously showed detection of echogenicity for > 20 s correlated 100% with injury.[15] In addition, the bladder fragmentation was readily observed in real time, and all three stones appeared to fragment completely within 3 minutes. In the kidney and bladder, BWL pulses enhanced the brightness of the Doppler twinkling artifact on the US image of the stone. In the kidney, fragmentation was not as observable during BWL because the stone and pieces filled a calyx and did not move, but fragmentation was made obvious on the Propulse 1 ultrasound image by separating the fragments with one pulse of ultrasonic propulsion. Video screen shots during breaking and repositioning were presented in the talk and can be viewed through the hyperlinks; twinkling artifact on the left of the screen highlights the stone in green color,[16] B-mode is on the right, and controls are on the lower half. Additional videos are available at apl.uw.edu/pushingstones.

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4. CONCLUSION

We report work toward an office-based, handheld ultrasound device to target, detach, break, and reposition stones and stone fragments in the urinary space to facilitate natural clearance. We have developed systems for imaging, breaking, and repositioning stones. Repositioning of stones has been safe and effective in humans. Breaking of stones with specific burst wave lithotripsy parameters is safe and effective in animal studies, and these data have been submitted in an application for an investigational device exemption for human trials.

In addition, our research group has developed the tools and approaches to continue to refine, expand, and test use of an integrated device. Specifically, we are working to develop advanced acoustic feedback (e.g., cavitation feedback[15]) and an understanding of how to use that feedback to adjust treatment parameters to enhance effectiveness of treatment without compromising safety. For instance, the stones targeted here were within the beam width of our probe, and it may be desirable to break larger stones. Fortunately, there remains considerable room to to continue to improve effectiveness and expand the application. For example, Tamaddoni and Hall,[17] in this session described a technology to control cavitation, and Zwaschka et al.[18] showed addition of weak ultrasonic propulsion pulses to BWL accelerated the comminution rate threefold.

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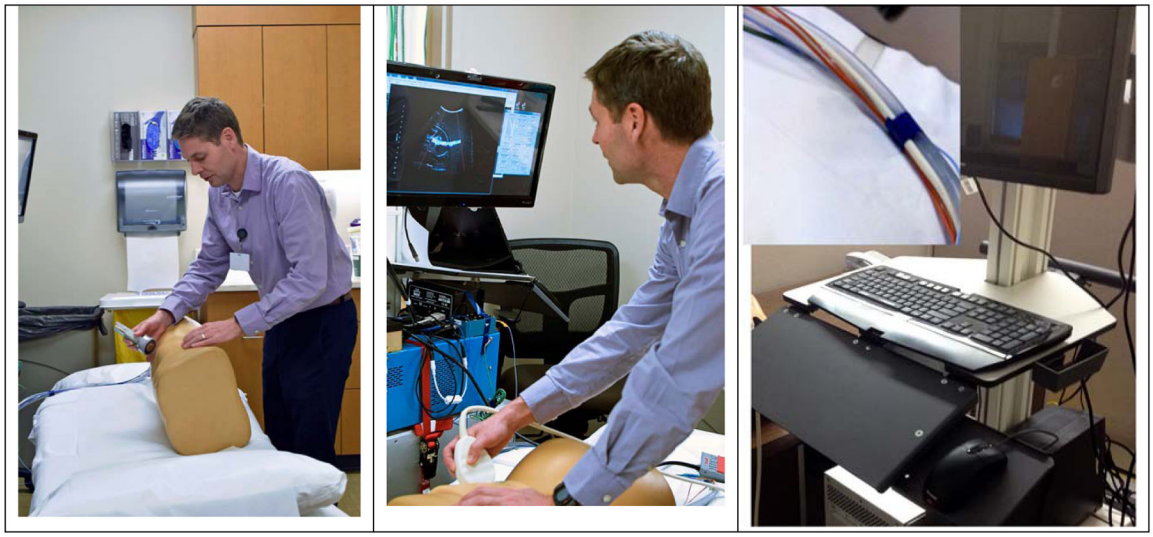

Figure 1:
Photographs of the University of Washington integrated stone imaging, breaking, and repositioning system. The inset with the handheld probe shows the rectangular imaging transducer surrounded by the circular therapy transducer.

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Table 1.

Summary of human studies of feasibility of ultrasonic propulsion.

Study	Status	Results
first feasibility	published[13]	**Purpose** Assess first feasibility **Materials and Methods** • therapy and imaging with Philips HDI C5–2 transducer • 13 of 15 were awake subjects • subjects with de novo stones, residual fragments, pre-surgery and during surgery. **Key Results** • moved stones in 14 of 15 subjects • depths up to 11 cm, stones as large as 10 mm • relieved obstruction pain 1 of 1 • 4 of 6 past surgery passed fragments • 4 large stones on clinical image were revealed to be passable fragment piles • No device-related adverse events.
During ureteroscopy (URS) surgery	15 of 19 subjects (16 of 20 kidneys) complete	**Purpose** Independent confirmation of movement of stones by imaging with a camera in the kidney. **Materials and Methods** • Stones were repositioned by ultrasonic propulsion with a handheld probe against the skin while observing with the ureteroscope during surgery. • Ultrasound and URS videos were sent to independent reviewers blinded to the exposure conditions to score movement greater than 3 mm, which was determined as a clearly resolvable displacement. **Key Results** • Independently confirmed motion >3mm in 15 of 16 kidneys • The video quality was too poor in the 16th case to make a determination. • Twice obviated the need for a basket to reposition stones • No serious or unanticipated adverse events. • Skin reddening (3), skin bruising (1), and skin irritation (1) were considered related to the propulsion procedure. • hematuria, nausea, changes in voiding and bowel habits, and pain/discomfort, considered related to URS and not ultrasonic propulsion.
symptomatic stones in the emergency department (ED) or acute setting	4 of 20 subjects complete	**Purpose** Move a symptomatic stone in the ureter with the goal of moving a small stone into the bladder or a large stone back into the kidney to relieve pain. **Materials and Methods** • Subjects with a symptomatic stone in the ureteropelvic junction (UPJ) or ureterovesical junction (UVJ) are recruited in the ED. • Movement and hydronephrosis are assessed from US images before and after by a radiologist blinded to the exposure conditions. • No treatment is withheld from the subjects. **Initial Results** • Moved 1 of 2 UPJ stones >3mm to a new location back toward the kidney. • Moved 1 of 2 UVJ stones < 3mm and same patient (1 of 2) passed the stone within 24 hours. • No devic- related adverse events.

Study	Status	Results
Randomized clinical trial to facilitate clearance of residual fragments	21 of 60 complete (13 of 30 treatment arm and 8 of 30 control arm)	**Purpose** Test clinical benefit of expelling residual fragments **Materials and Methods** • Subjects with residual fragments remaining >1 month after surgery. • Subjects are followed every 6 months for 3 years for recurrence. **Initial Results** • 13 of 30 recruited in the treatment arm • 8 of 30 recruited in in the control arm • (Also de novo stones in 1 subject were repositioned; the subject passed the stone that evening and more the next day.) • Early interim results reported to NIH and FDA are encouraging but are not reported here because they are interim.

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Table 2.

Summary of preclinical studies of safety and effectiveness of BWL.

Animal, Test Type	Test Description	Results
Porcine model, 7-day survival Safety	Clinical Simulation safety	**Purpose** Assess for acute and long term effects of clinical treatment **Materials and Methods** • 10 animals including 6 treatment and 4 controls • All groups split evenly between male and female • 1 treatment site in either left (n = 2) or right (n = 4) kidney • Dose: 30 min treatments at 350 kHz transmit frequency, 24 cycle pulse duration, 10 Hz PRF, and 7 MPa PNP **Key Results** • No significant histological changes to the kidney or other potentially intervening tissues • All blood chemistry, hematology, and urine values were within the expected normal limits for outbred swine • No animals displayed adverse clinical signs and the ultrasound therapy was well tolerated
Porcine model, Acute	Clinical Simulation effectiveness	**Purpose** Test the ability to break stones with the proposed clinical system and dose in a porcine model **Materials and Methods** • 7 stones (4–7 mm) implanted across 3 bladders and 1 stone in 1 kidney • 10–25 min treatments at 350 kHz transmit frequency, 20 cycle pulse duration, 17 Hz PRF, and 6 MPa PNP **Key Results** • No fragment recovered > 2 mm in 8 of 8 cases • No gross injury observed