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Focused Ultrasound to Expel Calculi from the Kidney: Safety and Efficacy of a Clinical Prototype Device

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Abstract

Purpose—Focused ultrasound has the potential to expel small stones or residual stone fragments from the kidney, or move obstructing stones to a nonobstructing location. We evaluated the efficacy and safety of ultrasonic propulsion in a live porcine model.

Materials and Methods—Calcium oxalate monohydrate kidney stones and laboratory model stones (2 to 8 mm) were ureteroscopically implanted in the renal pelvicalyceal system of 12 kidneys in a total of 8 domestic swine. Transcutaneous ultrasonic propulsion was performed using an HDI C5-2 imaging transducer (ATL/Philips, Bothell, Washington) and the Verasonics® diagnostic ultrasound platform. Successful stone relocation was defined as stone movement from the calyx to the renal pelvis, ureteropelvic junction or proximal ureter. Efficacy and procedure time was determined. Three blinded experts evaluated histological injury to the kidney in the control, sham treatment and treatment arms.

Results—All 26 stones were observed to move during treatment and 17 (65%) were relocated successfully to the renal pelvis (3), ureteropelvic junction (2) or ureter (12). Average $\pm$ SD successful procedure time was 14 ± 8 minutes and a mean of 23 ± 16 ultrasound bursts, each about 1 second in duration, were required. There was no evidence of gross or histological injury to the renal parenchyma in kidneys exposed to 20 bursts (1 second in duration at 33-second intervals) at the same output ($2,400 \text{ W/cm}^2$) used to push stones.

Conclusions—Noninvasive transcutaneous ultrasonic propulsion is a safe, effective and time efficient means to relocate calyceal stones to the renal pelvis, ureteropelvic junction or ureter. This technology holds promise as a useful adjunct to surgical management for renal calculi.

Keywords

kidney; kidney calculi; ultrasonography; lithotripsy; ureteroscopy

The prevalence of kidney stone disease is increasing and it was recently estimated to affect almost 9% of the American population.¹ Approximately 50% of newly diagnosed patients have a recurrent symptomatic stone within 5 to 10 years.² The various aspects of stone evaluation and management can be costly and they have been described internationally.^{3,4} Although effective minimally invasive treatment options exist, residual stone fragments are not uncommon after treatment and they may grow with time and/or become symptomatic.^{5–9} In general, the most troublesome stone site is the lower pole since fragments at this location have a lower clearance rate.^{10–13}

Our group previously reported the ability to use noninvasive, focused ultrasound technology to move urinary tract calculi in a phantom model and subsequently in the porcine kidney.^{14,15} This demonstrated proof of concept for using ultrasonic propulsion to facilitate the clearance of lower pole residual stone fragments. Several advancements and modifications have since been achieved. In this study we assessed a new prototype device for treatment efficacy in relocating calyceal stones to the renal pelvis, UPJ and proximal ureter. We also assessed evidence of kidney injury in a porcine model.

MATERIALS AND METHODS

Our clinical prototype incorporates several improvements over the initial research device, which was described previously.^{14,15} Figure 1 shows the 2 systems. With the new prototype all imaging and therapy are completed with a single ultrasound imaging probe HDI C5-2 or P4-1 probe (ATL/Philips), 1 ultrasound engine (Verasonics), 1 computer processor and 1 display monitor. The screen displays a real-time ultrasound image of the kidney and stone. The user targets the stone, fires the ultrasound source and observes stone movement by identifying the stone position on the screen.

Acoustic energy was decreased from the original study and it is lower than that used for SWL. Table 1 shows the peak pressure and energy dose of SWL and our prototype measured in water according to regulatory standards.^{16–19} Energy dose is the product of the maximum number of pulses (n) and the derived acoustic pulse energy in a focal cross section 12 mm in diameter ($E_{\text{eff}}[12 \text{ mm}]$).^{16–19} Our system uses 20 to 40 push bursts. Each push burst duration of 0 to 1 second is selected by the user. A 1-second push burst delivers almost 250 finely focused pulses 0.1 millisecond in duration with 200 shocks. Pressure and energy are about a half and a quarter, respectively, the values of many current shock wave lithotripters. These differences are likely greater in situ since tissue attenuates the 2 MHz signal an order of magnitude more than a standard lower frequency SWL pulse.

Studies

Efficacy—All animal studies were approved by the University of Washington institutional animal care and use committee. Ureteroscopy was performed using general anesthesia on 14 kidneys from a total of 8 common domestic female pigs weighing 50 to 60 kg. A 2.5 mm

silver coated glass reference bead was endoscopically placed in an upper pole calyx using a nitinol basket. A series of 2 to 8 mm stones (calcium oxalate monohydrate coated in tantalum powder) or beads were implanted in interpolar or lower pole calyces for ultrasonic repositioning. Stones were coated to improve visualization under fluoroscopy. Stone position was confirmed under direct visual guidance by ureteroscopy and by fluoroscopy.

Stones were targeted by transcutaneous ultrasound using the same transducer used subsequently for ultrasonic propulsion to push the stone. Push bursts were delivered by touching the image of the stone on the monitor. The goal was to displace stones from the original position in a renal calyx to the renal pelvis, UPJ or ureter. Stone motion was visualized and recorded using fluoroscopy with an OEC® 9800 device under direct ureteroscopic guidance and with the ultrasound imager in real time. If several attempts to push the stone were unsuccessful, the probe was moved to a different angle, and targeting and treatment were repeated. If these maneuvers were unsuccessful, the pig was repositioned and the procedure was repeated.

Device settings and output parameters were recorded for each push burst attempt. Data included output voltage, push burst duration, location of the focus seen in the image selected by the user and raw images converted to video.

The primary outcome was stone clearance, defined as stone displacement to the renal pelvis, UPJ or ureter. Secondary outcomes included mean procedure time, number of push burst attempts and total time of exposure to push bursts. As an approximate measure of stone movement, the difference in stone locations was measured using pretreatment and posttreatment fluoroscopic images, recognizing that the actual path of displacement was often longer.

Safety—Nine kidneys from a total of 6 anesthetized female pigs were randomized to control, sham and treatment groups. To avoid a potentially confounding iatrogenic injury, no invasive endoscopic procedures were done in these animals. The control group was anesthetized but received no ultrasound or treatment. The sham treated group underwent ultrasound visualization but was not treated with ultrasonic propulsion. The treatment group underwent simulated conditions of maximum clinical exposure to ultrasonic push burst energy with the probe directed toward the lower pole calyx, ie the same maximum pressures and intensities used in the efficacy study but 36 bursts compared to the mean of 23 during the efficacy study (table 1). Settings for maximum clinical exposure (36, 1-second push bursts at 33-second intervals during 20 minutes with an output of 2,400 W/cm²) were determined from the efficacy study. Urine and venous blood samples were collected before and immediately after treatment.

Histopathological Analysis

The 9 kidneys from the safety study were prepared for histopathological analysis by light microscopy. After sacrifice, the kidneys and all tissues in the acoustic path were immersion fixed in 10% neutral buffered formalin and routinely processed for paraffin embedding. Sections (5 μ m) were stained with hematoxylin and eosin. Before fixation, each kidney was serially sectioned to ensure adequate fixative penetration. Fixed kidneys were sampled from

6 areas in the target region as well as representative areas in the entire kidney. Three observers blinded to experimental conditions independently assessed the specimens for injury. Histological evaluation was performed to identify tubular cell damage, ruptured blood vessels, coagulative necrosis and tissue emulsification injury patterns.

RESULTS

Efficacy

Stones were successfully placed in 12 of 14 kidneys. Experimental time constraints along with anatomical difficulties prevented placement in 2 kidneys. A total of 26 natural and artificial stones were placed in interpolar and lower pole calyces (2 to 3 per kidney) as targets for relocation. All stones were visible on ultrasound and all stones exposed to ultrasonic propulsion were observed to move in the calyx. Overall, 17 of 26 stones (65%) were successfully relocated from the calyx to the renal pelvis (3), UPJ (2) or ureter (12) (table 2). Stone size did not appear to be associated with successful repositioning. Two calculi were moved out of the calyx but did not reach the renal pelvis. The remaining 7 stones were observed to move upon exposure to push bursts but were not dislodged from the calyx. Figure 2 shows select images of a successful push.

Average $\pm$ SD procedure time to successfully displace a stone was 14.2 ± 7.9 minutes and a mean of 23 ± 16 push bursts was required (table 2). Push bursts averaged 0.9 seconds in duration with none greater than 1 second. They were separated by a mean of 41 ± 13 seconds. Most push attempts did not move the stone or, less commonly, the stone moved but fell back into the same calyx. In contrast, few effective pushes were necessary to result in stone clearance. When the stone was inadvertently repositioned into an upper pole calyx, it was possible to push the stone back toward the UPJ. Average estimated displacement was 5.6 ± 2.7 linear cm when comparing fluoroscopic images before and after treatment.

Safety

Gross hematuria was not observed in any experimental group. Creatinine was normal in all pigs based on known reference values for the porcine model.²⁰ Thorough histological analysis of the targeted regions of treated kidneys as well as the renal parenchyma outside the treatment zone and adjacent organs showed no evidence of structural damage (fig. 3). The renal parenchyma was uniformly intact and contained no ruptured blood vessels or broken renal tubules. Also, there were no lesions suggestive of thermal necrosis in the treated kidneys. Overall, the morphology of kidneys treated with ultrasonic propulsion was indistinguishable from that of the kidneys of untreated control and sham treated pigs.

DISCUSSION

Nephrolithiasis is a worldwide disease with significant economic impact.^{3,4,21} In the United States the prevalence increased from 5.2% to 8.8% in the last 20 years, while total expenditure was estimated to be greater than \$2.1 billion in 2000 with costs even greater when including indirect costs such as missed work.^{1,3,21,22} Since many of these patients eventually require surgical treatment for calculi, the ideal outcome is to become stone free.

Although surgical procedures for stone removal tend to be effective, residual fragments often remain and can be problematic. Endoscopic equipment has improved in the last decade but a prior randomized trial showed a stone-free rate of only 50% after ureteroscopy and 35% after SWL for lower pole calculi less than 1 cm.¹² The natural history of residual stone fragments was described after various treatment modalities and it may be associated with significant morbidity from symptomatic episodes and the need for reintervention.^{9,23,24} Residual stones after SWL have required re-treatment at 5 years in 21% to 52% of cases.^{5,6,25} Methods intended to clear these fragments have been described, such as mechanical percussion, inversion therapy and diuresis, although with limited success.^{26–29}

Experimental outcomes of our clinical prototype acoustic propulsion device were encouraging. All treated stones were observed to move, and 65% of interpolar and lower pole stones were successfully moved from the calyx to the renal pelvis, UPJ or ureter using ultrasonic propulsion. Although calcium oxalate calculi were used in this study, composition is not believed to be a limiting factor since we previously displaced mixed calcium, calcium phosphate and cystine stones.¹⁴ This modality appears to be safe and without histological evidence of renal injury. Minimal to no injury might be expected, given that the acoustic pressure and energy are lower than those used currently for SWL (table 1).

While blood studies did not indicate kidney injury, serum creatinine is not a sensitive test for minor kidney injury. In preparation for application for Food and Drug Administration (FDA) approval and a subsequent human clinical trial, at least 25 additional treated kidneys were evaluated histologically without concerning tissue injury (unpublished data).

We envision several potential clinical applications of this technology in the outpatient and operative settings, including as an adjunct to primary medical expulsive therapy for small stones or after lithotripsy to clear residual fragments. The clearance of small stones may prevent calculus growth and avoid an unpredictable acute stone event. The device may also have a role in the management of acute renal colic due to an obstructing UPJ stone by pushing the stone back into a nonobstructing position in the kidney. This would avoid an urgent operative procedure and allow for treatment in an elective setting. Current research is under way to test this scenario. Additional applications may include intraoperative repositioning of stones during ureteroscopy or percutaneous nephrostolithotomy to enable the extraction or treatment of calculi that are difficult to reach.

Like any endourological procedure, there will be a learning curve to become proficient with focused ultrasonic propulsion. Effective targeting to push stones requires good stone visualization and alignment with a path for the stone to travel. Calculi that are difficult to see on ultrasound are also likely to be difficult to reposition, although the capability to elicit movement of a suspect stone with ultrasound could be of diagnostic value. While the average treatment time to successfully displace a stone was 14.2 minutes and required 23 push bursts, after the stone moved, only a few well targeted hits were required to achieve stone clearance. This further highlights the importance of ultrasound proficiency to help overcome the learning curve. In our observations pulses that did not relocate the stone toward the UPJ or ureter appeared limited by the alignment angle of ultrasound forces and not due to inadequate force generation.

This technology was designed for urologists to treat patients with stone disease. However, not all urologists routinely perform renal ultrasound in the office. An experienced ultrasonographer was used during this study to image and target calculi. Ultrasound courses for urologists are available to teach diagnostic skills and image interpretation. With this technology additional skill appears to be required to position, align and target the stone. Efforts are under way to develop a curriculum using phantom models to train urologists to use this device. Our team is also performing research to improve the ultrasound detection of stones, which would also benefit this application.

Our findings in this study must be interpreted in the context of the limitations of our study design using the porcine model. Retrograde ureteroscopy limited the size of the stone that could be placed and in some cases introduced air or caused minor bleeding, decreasing our ability to detect the stones and hindering stone movement. Collecting system dilatation was sometimes a result of implanting calculi in this manner, which theoretically may facilitate stone displacement. However, stones were also successfully displaced in nondilated systems. We recognize that the collecting system and ureters of humans are different from those of the porcine model.

Until human trials are performed, several questions remain unanswered. It is unclear how a greater skin to stone distance in humans would affect efficacy. Current modifications of the new device have allowed treatment at a 12 cm source-to-target distance. Since it is difficult to perform ultrasound in large patients, we envision the same challenges when using this technology with increasing body mass index. While the device appears safe in the animal model, to our knowledge it is also unknown whether the treatment causes pain. Avoidance of anesthesia would be necessary for the device to be used in the outpatient setting. Due to the retrograde endoscopic approach used to implant calculi, the maximum size of treated stones was limited to 8 mm or less. To date the largest stone attempted in vivo was 11 mm, which was implanted through an open incision and moved successfully. Upper pole stones may be difficult to visualize and reposition due to the ribs and adjacent organs. It would also be of interest to see whether stones adherent to a papilla/ Randall plaque could be dislodged. While these and other questions remain, several advancements have improved this technology to overcome the limitations of the original research device.

CONCLUSIONS

Ultrasonic propulsion was an effective, efficient and completely noninvasive method to relocate calyceal stones to the renal pelvis or ureter in the porcine model. The acoustic forces generated to reposition calculi appear to be below the injury threshold since thorough histological analysis revealed no evidence of injury to the kidney. We are pursuing FDA approval for a human feasibility study in the United States to test the device in patients with de novo stones or residual stone fragments after lithotripsy.

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Abbreviations and Acronyms

SWL	shock wave lithotripsy
UPJ	ureteropelvic junction

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Figure 1.

A, first generation device with HDI5000 diagnostic ultrasound, cooling system, transducer (arrow) and acoustic propulsion hardware with laptop. *B*, second generation device with Verasonics ultrasound engine, desktop computer and Philips/ATL transducer (inset).

Figure 2.

Select real-time B-mode images. Blue arrow indicates stone and stone motion direction in collecting system. After targeting (red dot), single burst of ultrasound pulses is applied and stone makes single movement from calyx to proximal ureter. All motion occurs in approximately 1 second.

Figure 3.
Porcine renal histology. *A*, control. *B*, treated. H&E, scale bar represents 200 μm .

Table 1

Published outputs of current shock wave lithotripters and our ultrasonic propulsion prototype

	Current Lithotripters	Prototype
Peak pressure (MPa)	37–115	20
Peak pulse intensity derated to 7 cm (W/cm ²)	Greater than 20,000	2,400
Energy dose at $n \times E_{\text{eff}}$ (12 mm) (J)	100–200 (2,000–4,000 pulses)	30–47 (23–36 bursts)

Table 2

Efficacy of ultrasonic propulsion prototype in successfully displaced stones

Pig No. (side)	No. Stones Implanted/No. Pushed (%)	No. Pushes	Total Treatment Time (mins)	% Time Pushing
1 (rt)	3/1 (33)	10	6.7	2.5
2 (lt)	2/2 (100)	94	50.8	3.1
3:				
Rt	2/1 (50)	18	15.8	1.9
Lt	2/2 (100)	56	40.0	2.3
4 (lt)	2/2 (100)	35	17.2	3.4
5:				
Rt	2/0	—	—	—
Lt	2/1 (50)	47	24.6	3.2
6 (rt)	2/1 (50)	9	2.0	3.3
7:				
Rt	2/1 (50)	10	9.8	0.5
Lt	2/2 (100)	22	20.9	1.6
8:				
Rt	3/2 (67)	20	18.0	1.2
Lt	<u>2/2 (100)</u>	68	36.2	2.5
Total	26/17 (65)			
Mean ± SD		22.9 ± 16.3	14.2 ± 7.9	2.3